A Dissertation on

"CAROTID INTIMA MEDIA THICKNESS AS A MARKER OF PRECLINICAL ATHEROSCLEROSIS IN TYPE 2 DIABETES MELLITUS" AT GOVERNMENT STANLEY HOSPITAL, CHENNAI-600001.

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY CHENNAI – 600032.

In partial fulfillment of the Regulations for the
Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE CHENNAI – 600 001

APRIL -2016

CERTIFICATE BY INSTITUTION

This is to certify that **Dr. G.AYYAPPAN,** Post - Graduate Student (MAY 2013 TO APRIL 2016) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600001, has done this dissertation on "**CAROTID INTIMA MEDIA THICKNESS AS A MARKER OF PRECLINICAL ATHEROSCLEROSIS IN TYPE 2 DIABETES MELLITUS"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2016.

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DECLARATION

I **Dr.G.AYYAPPAN** declare that I carried out this work " **CAROTID INTIMA MEDIA THICKNESS AS A MARKER OF PRECLINICAL ATHEROSCLEROSIS IN TYPE 2 DIABETES MELLITUS"** at the medical ward and Medical OPD, Government Stanley Hospital during the period March 2015 to August 2015. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M. D. Degree examination in General Medicine.

Dr. G. AYYAPPAN

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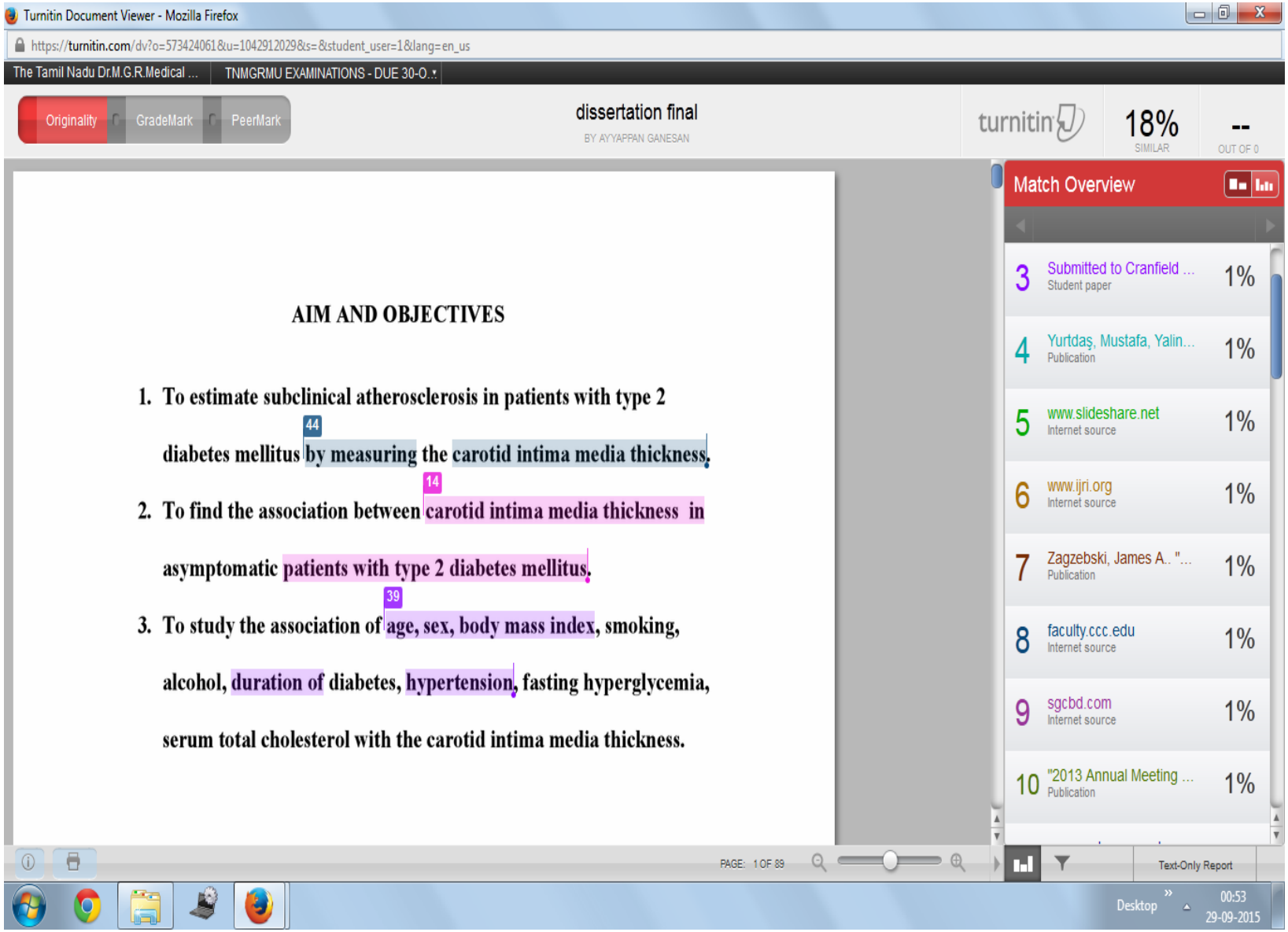
Last but not the least; I sincerely thank all those **patients** who participated in this study, for their co-operation.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1. To estimate subclinical atherosclerosis in patients with type 2 diabetes mellitus by measuring the carotid intima media thickness.
2. To find the association between carotid intima media thickness in asymptomatic patients with type 2 diabetes mellitus.
3. To study the association of age, sex, body mass index, smoking, alcohol, duration of diabetes, hypertension, fasting hyperglycemia, serum total cholesterol with the carotid intima media thickness.
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AIM AND OBJECTIVES

1. To estimate subclinical atherosclerosis in patients with type 2 diabetes mellitus by measuring the carotid intima media thickness.
2. To find the association between carotid intima media thickness in asymptomatic patients with type 2 diabetes mellitus.
3. To study the association of age, sex, body mass index, smoking, alcohol, duration of diabetes, hypertension, fasting hyperglycemia, serum total cholesterol with the carotid intima media thickness.

Place of study

Dept of Medicine, Stanley Medical College and Hospital

Study population

50 patients of TYPE 2 Diabetics

Study design-

Descriptive study

OPERATIONAL DEFINITION

CASE DEFINITION:

- The determination of type 2 diabetes was based on ADA 2014 guidelines, which defines the diagnosis of Diabetes Mellitus as follows:

1. Symptoms of diabetes plus random blood glucose> 200 mg/dl (or)
2. Fasting plasma glucose>126mg/dl (or)
3. Two-hour plasma glucose>200mg/dl during an oral GTT.

Carotid IMT :

- It was measured on both sides and the average value was taken as the mean CIMT.IMT value of more than 0.9 mm is suggestive of significant atherosclerosis

INCLUSION CRITERIA

- Asymptomatic individuals attending the outpatient department of medicine and medical ward diagnosed with type 2 diabetes mellitus according to ADA 2014 guidelines were included in the study if they met the following inclusion criteria.
- Diagnosis of diabetes after 30 years of age

EXCLUSION CRITERIA

1. Those having acute metabolic complications like hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycaemic state, cerebrovascular accidents, acute infections, inherited disorders of lipid and lipoprotein metabolism and/or family history of such disorders and deranged liver functions were excluded.
2. Patients on lipid lowering treatment
3. Previous history of CABG or PCI intervention.
4. Acute stage or signs and symptoms of CHD / cerebro vascular disease after careful evaluation of clinical records.
5. Age more than 60 years
6. Hypertensive patients

METHODOLOGY

- Selected sociodemographic, clinical and laboratory data will be collected from the cases and will be recorded in a pro forma.
- Socio demographic data will comprise of:

  age ,sex ,locality,occupation

- Clinical data will comprise of:

- History of Diabetes, hypertension

- History of smoking, alcohol

- Height, weight and BMI

- General and systemic examination

Examination of peripheral pulses and BP recording in all 4 limbs with

- Laboratory data to be included:

- Urine - albumin, deposits, Sugar

- Fasting Blood Sugar

- Blood Urea

- Serum Creatinine

- Fasting Serum Total Cholesterol

- ECG

IMAGING STUDIES

- CAROTID INTIMA MEDIA THICKNESS by Doppler
- 50 consecutive type 2 diabetic patients (diagnosed by the ADA 2014 criteria) among the outpatients attending department of medicine will be subjected to detailed history, physical examination, BP recording in all 4

limbs, examination of all peripheral pulses, height, weight and calculated BMI(weight in kg / height in metre square).

- Baseline laboratory data, resting 12-lead ECG, and CIMT measurement will be collected for each patient. Fasting blood sample will be obtained, and measurement of serum total cholesterol, serum creatinine, blood urea, and blood sugar will be made by standard laboratory techniques.
- Blood pressure will be measured with a standard mercury sphygmomanometer.
- Hypertension is defined as a systolic blood pressure >140 mmHg, a diastolic blood pressure >90 mmHg, in accordance with JNC VIII criteria.
- Hyperlipidemia is considered to be present when the patient had a serum total cholesterol level >200 mg/dl.

ASSESSMENT OF CAROTID INTIMA MEDIA THICKNESS

- Ultrasonographic scanning of the carotid arteries will be performed using Esoate – scanner with a linear transducer (high frequency range 10 to 12 MHz).
- The patient being in supine position and chest being elevated with a pillow and the head being turned to the opposite side of the carotids to be examined. The probe will be placed on the medial side of the

sternocleidomastoid muscle to identify the carotid vessel and the carotid bulb will be traced.

- Intima media thickness will be assessed at about 1.0 cm proximal to the carotid bulb.
- The carotid wall will show parallel echogenic lines separated by a hypoechoic region (media). The inner line is the lumen – intima interface and the outer is the media – adventitia interface.
- Carotid IMT is defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans. Carotid IMT is measured on both sides and the average value is taken as the mean CIMT.IMT value of more than 0.9 mm is suggestive of significant atherosclerosis.
- The study period is from march 2015 to august 2015.

STATISTICS

- Descriptive statistics will be done for all data and suitable statistical tests of comparision will be done. Continuous variables will be analyzed with the unpaired t-test and categorical variables will be analyzed with the chi-square test with Yates correction. Statistical significance will be taken as $P< 0.05$.

HUMAN SUBJECT PROTECTION:

- The full protocol along with draft questionnaire and Informed consent will be kept in Institutional ethical Committee and approval will be obtained.

INFORMED CONSENT:

- Consent form will be written in both English and Tamil and consent will be obtained from the participant, confidentiality will be maintained.

Expected benefits from study:

- CIMT is easy non invasive technique, routine measurement of CIMT in DM helps in reducing morbidity and mortality from macro and microvascular complications. It helps us in diagnosing atherosclerosis in the earliest stages and enable us take preventive measures to prevent the complication of atherosclerosis.

INTRODUCTION

Atherosclerosis is a leading cause of mortality in developed and developing nations. In another two decades cardiovascular diseases complicated by atherosclerosis will be the major cause of death. Supported by major and minor risk factors and non modifiable and modifiable risk factors. Atherosclerosis forms the major determinant in the reduction of volume of vascular lumen in various parts of the blood vessel. Acute coronary syndrome includes two entities namely myocardial infarction and angina pectoris has chief involvement of atherosclerosis in it. [1]

Diabetic population is expected to reach an epidemicproportion in many of the countries around the world and it has greatly accelerated the risk for cardiovascular diseases and early mortality. Hence management of diabetes is really a great challenge in the society.

Prevalence of T2DM was found to be around 380million in 2013 and is expected to be around 600million in year 2035

Diabetes Mellitus

DEFINITION

Diabetes mellitus is a metabolic disorder with a polygenic aetiology characterised by deranged metabolism of carbohydrate fat and protein, with chronic altered blood sugar status with alteration in insulin secretion, mechanism of action or combination of both of the above. [23].

INSULIN ORIGIN AND EVOLVEMENT [22]

1921 Demonstration of pancreatic extracts in experimental diabetic dogs shown to reduce blood sugar

1922 Insulin used for the first time in humans

1923 Large quantities of potent insulin were produced from animal sources

1925 International units were described for insulin

1926 Generation of amorphous crystalline stable insulin

1936 Duration of insulin was prolonged by addition of zinc to protamine insulin

1939Invention of short acting insulin

1950 NPH insulin was developed

1951 Lente insulin was made by buffering acetate with zinc

1955Complete insulin structure was defined

1966 Radioimmuno assay of insulin was done

1967 Discovery of proinsulin

1967 First pancreatic transplant

The criteria for the diagnosis and classification of diabetes have continued to evolve with the accumulation of new knowledge. In the year 1997 an expert committee for

classification and diagnosis of diabetes modified and they updated the 1979 report and then modified in 1999 to make some changes in the diagnosis of gestational diabetes.

One of the major changes in 1997 was the increased emphasis upon fasting plasma glucose levels, with the cut-off for diabetes being lowered to 126 mg/dl from the earlier value of 140 mg/dl.

MONITORING OF CAPILLARY BLOOD GLUCOSE

In 1970 the urine blood sugar was replaced by self monitored blood glucose estimation

"Benedict" urine test introduced in 1911[22]

GLYCOSYLATED HEMOGLOBIN

In the late 1970s, the glycosylated haemoglobin assay gained rapid application.

DIABETES – CLASSIFICATION [23]

I. Type 1 Diabetes mellitus (complete cell destruction, leads to absolute insulin loss)
   A. Immune-mediated destruction
   B. Idiopathic aetiology

II. Type 2 diabetes mellitus (has combination of insulin resistance with Some insulin deficiency to a dominantly insulin synthesis defect with insulin resistance)

III. Other sub- types of diabetes mellitus
   A. Genetic alterations in cell function which manifests by mutations in:
   1. Hepatocyte nuclear transcription factor(MODY TYPE 1)

2. Glucokinase (MODY TYPE 2)
3. HNF-1 (MODY 3)
4. Insulin promoter factor-1 (MODY 4)
5. HNF-1 (MODY 5)
6. NeuroD1 (MODY 6)
7. Mitochondrial DNA
8. Subunits for ATP-sensitive potassium channel

B. Genetic abnormalities in insulin action
   1. Type A insulin resistance
   2. Leprechaunism
   3. Rabson-Mendenhall syndrome
   4. Lipodystrophy syndromes

C. Diseases of the exocrine pancreas – eg..pancreatitis, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy

D. Endocrinopathies - includes acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism etc

E. Drugs and chemicals — pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, adrenergic agonists, thiazides, phenytoin, interferon, protease inhibitors, clozapine.

F. Infections—congenital rubella, coxsackie virus,

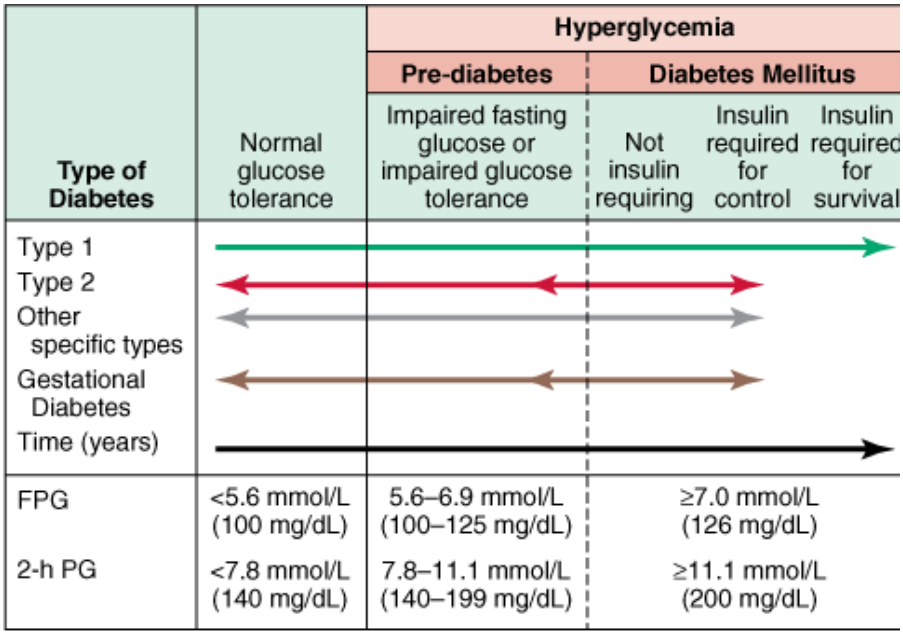
G. Other genetic syndromes associated with diabetes— Turner's syndrome,

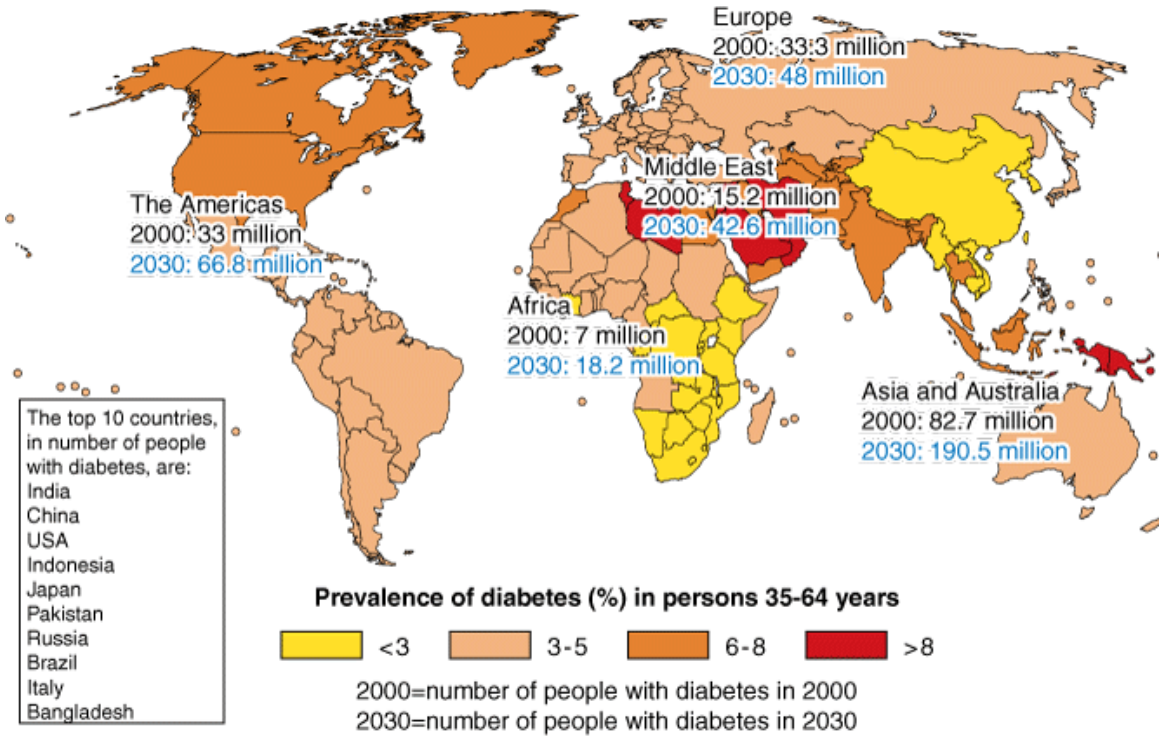
Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, Prader-Willi syndrome,klinefelters and turners syndrome.

IV. **Gestational diabetes[23]**

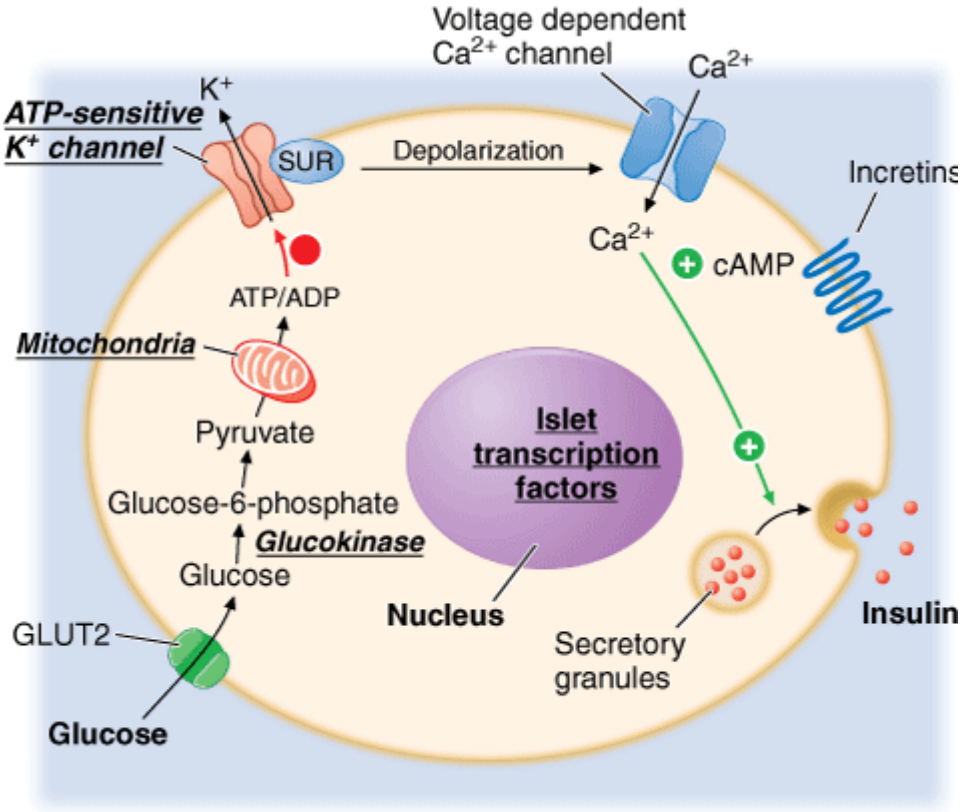
Risk Factors implicated in Diabetes[17]

- Family history of diabetes mellitus
- People with Impaired fasting or post prandial glucose values
- physical inactivity
- overweight
- Race/ethnicity
- Hypertension
- Low HDL cholesterol and high triglyceride level(greater than 250 mg)
- History of Gestational DM or an overweight new born baby
- Polycystic ovarian disease.

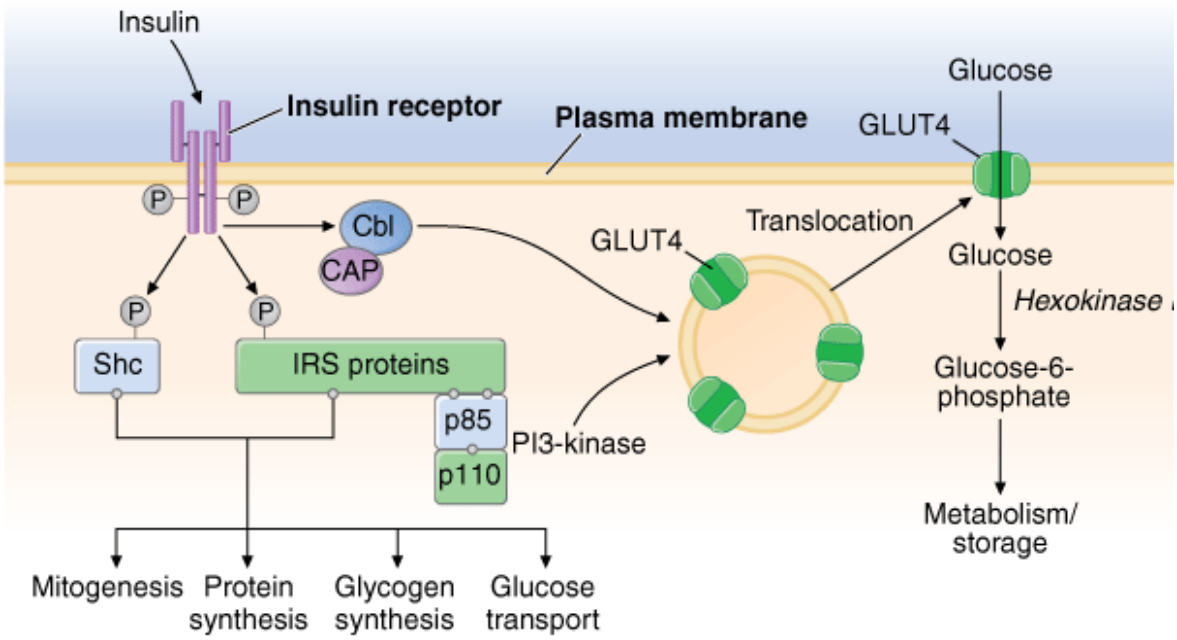




PHYSIOLOGY OF INSULIN SECRETION



MECHANISM OF INSULIN ACTION



COMPLICATIONS OF DIABETES [24]

ACUTE METABOLIC

1.Diabetic ketoacidosis[DKA]

2. Hyperosmolar Nonketotic diabetic coma.

3.Hypoglycemia.

4.Lactic acidosis

Chronic Complications

1. Micro Vascular

2 Diabetic retinopathy(non proliferative & proliferative)

3. Cataract

4. Glaucoma

Neuropathy

i)Sensory

ii) Motor

iii) Sensory Motor

iv) Autonomic

Nephropathy

i) Microalbuminuria

ii)Macroalbuminuria

iii) Chronic kidney disease

Larger vascular lesions

- Coronary artery disease
- Peripheral Vessel disease
- Cerebrovascular disease

Other possibilities [24]

- Gastroparesis

Diabetic ketoacidosis (DKA) & Hyperosmolar hyperglycemic state (HHS)[40]

Hyperosmolar hyperglycemic state or non ketotic hyperosmolar coma and diabetic ketoacidosis signify two distinct metabolic syndromes depicted by insulin deficiency and high blood sugar.

HHS occurs when insulin deficiency relative to insulin requirements causes hyperglycemia, which in turn leads to dehydration, ultimately resulting in a severe hyperosmolar state.

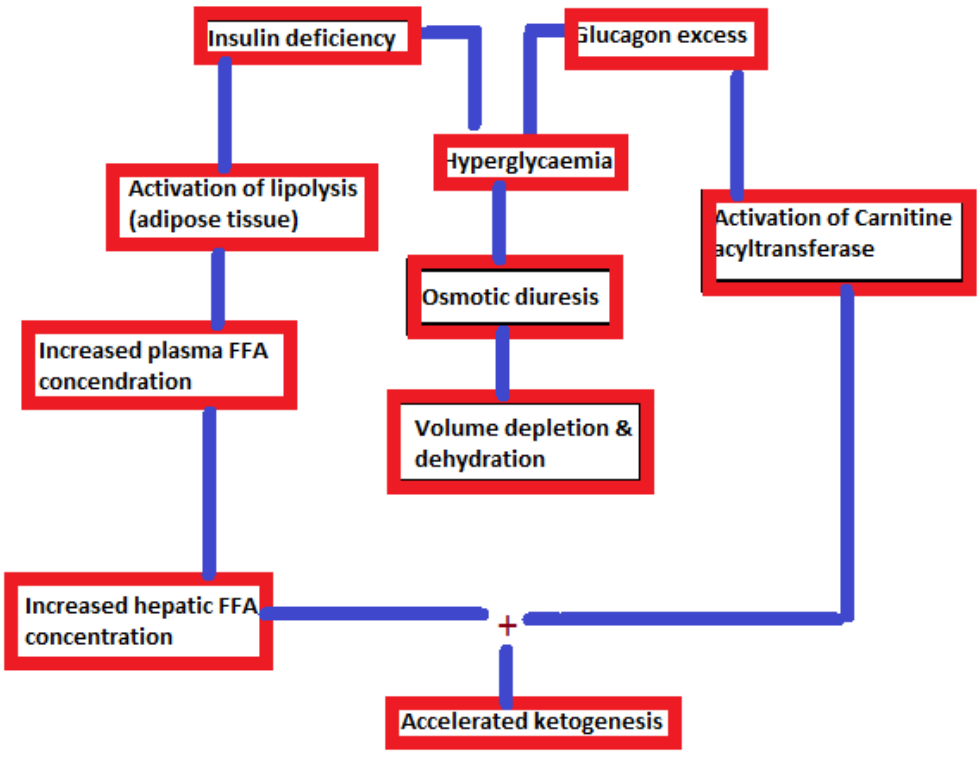
DKA should include three cardinal features hyperglycemia (blood glucose >250 mg/dL), ketogenesis, and

(iii) acidosis (pH <7.35)

HHS manifests by extremely high blood sugar (more than 600 mgs) and osmolarity greater than 290 mosm.

Both are due to insulin deficiency. often both of them can co exist or both can occur simultaneously and also patients exhibit features of both the syndromes.

Pathogenesis of DKA[40]



Precipitating Factors

- Infections(MC UTI,PNEUMONIA)
- Myocardial infarction,CVA
- Pancreatitis
- Alcohol abuse,
- Drugs-Steroids,Thiazides,Ribavirin,Interferon alpha,Olanzapine

SYMPTOMS AND SIGNS IN DKA[40]

- Nausea, shortness of breath,
- Frequent urination,
- Excess Thirst,
- Diffuse Abdominal pain.
- Heart rate >100 per min
- Dehydration – dry skin,conjunctiva,dry tongue
- Fall in blood pressure,
- Increased respiratory rate(Kussmaul breathing)

TREATMENT OF DKA[43]

1. Test to prove the diagnosis(plasma glucose,blood ketones, ABG-high anion gap metabolic acidosis).
2. Intensive care , monitoring of pH and GCS is important
3. check :Electrolytes (sodium,Hco3,potassium,magnesium,chloride,phosphate)

   ABG-- PCO2, Ketones--- b-hydroxybutyrate,blood urea ,serum creatinine

   Every hour
4. fluid replacement: 2 L of normal saline is given during first hour (at a rate of 15 to 20 mL/kg per hour); Followed by normal saline or half NS is given at a rate of 5 to 15 ml per kg/hr; The fluid is changed to dextrose normal saline when the blood sugar reaches 250 mgs.
5. Insulin administration:

Short acting (regular insulin) started as 0.14units per kg IV bolus followed by 0.1 units per kg per hour infusion. serum potassium and blood sugar are monitored hourly. Insulin should not be started if serum potassium is less than 3.3meq because insulin drives more potassium inside the cell precipitating more profound hypokalemia.

6. Find the precipitating cause for DKA eg.infections,trauma,insulin withdrawal,infarction etc. Do investigation to get the precipitating factor like cultures,ecg etc.
7. Hourly measurement of capillary blood glucose is done and measurement of electrolytes viz sodium,magnesium,potassium,chloride,anion gap,bicarbonate is done once in every four hours.
8. Assess fluid status and urine output every hour and also GCS scoring of the patient should be made hourly.
9. K+ replacement:

K+ infusion is given at 10meq /hr if serum potassium is less than 5.5meq when insulin has been started,further potassium infusion can at a rate beween 40 to 80 meq/hr if serum k+is less than 3.3meq.

10. All above measures are followed till patient becomes conscious,oriented,normalisation of acidosis and anion gap,blood sugar is less than 170 mgs,serum electrolytes are within normal limits. Now patient can be switched over to subcutaneous long and short acing insulin.

GUIDELINES FOR INSULIN THERAPY IN DKA AND HHS[44]

- Short acting insulin 0.15 U/kg i.v. stat initially.
- Initial stat dose is followed by regular insulin infusion at 0.1 U/kg per hour.
- Insulin dose is increased by 1 U per hour for every 1hr in case if there is less than 10 percent decrease in glucose values.
- Rate of infusion is titrated by 0.05–0.1 U/kg per hour when glucose ≤250 mg/dL and when

there is improvement in clinical signs with decline in sugar of >75 mg/dl per hour.

- Rate should not be reduced for not more than one unit per hour
- Sugar status is optimised between 140 and 180 mg/dL.
- If blood sugar falls to <80 mg/dL, stop infusion .
- If glucose reduces to <150 mg/dL, change IVF from normal saline to 10 percent dextrose to maintain blood sugar from 140 to 180 mg/dL.
- Subcutaneous insulin is started once patient becomes alert and starts to eat.

Intravenous insulin infusion and subcutaneous regimen should be continued for one to two hours.for known diabetic patients who were already on insulin the dose can be restarted. For others who are newly detected dose of insulin is stared at a dose of 0.6u per kg/day

Insulin should be hold at a potassium level of < 3.3 meq/l and to be restarted once level reached more than 3.5 meq/l. Pottasium should not be given if patient is oliguric/anuric.

Phosphate[53]

Loss of po4 occurs in DKA and HHS. Intracellular po4 is lost, and renal phosphate excretion is increased. During insulin therapy, phosphate is taken inside cells with resultant hypophosphatemia

Hypophosphatemia is associated with decreased cardiac dysfunction, respiratory muscle paralysis, muscle injury, reduced mental awareness, rarely involuntary movements and hemolysis. Intravenous phosphate therapy may lead to hypocalcemia. Thus, the degree of phosphate replacement and type of phosphate treatment required in DKA and HHS remain controversial. Po4 therapy is done only in case of severe hypophosphatemia or in whom serum calcium concentrations are normal.

Euglycemic DKA[42]

It was described in patients who were on subcutaneous insulin pumps containing regular

insulin (short acting agents like lispro) as the ingredient in the pump.

In these subjects when delivery of insulin is inhibited it results in faster development of ketone bodies and they will become deprived of insulin totally within 2 to 4 hours.

It is described in pregnant females and in people using conventional insulins Here normal sugar level is probably due to reduced release of hepatic glucose.

Treatment

Oral Hypoglycemic Agents[47]

Sulphonylureas

Mechanism of Action

Insulin secretagogues- they cause blocking of ATP sensitive potassium channels on the islet cells and thereby produce insulin secretion insulin .This leads to depolarization of membrane leading to influx of calcium.

Drug	**Daily dose(mg)**	**Doses/dy**	**Half-life(hours)**	**Metabolism / excretion**
First generation				
Acetohexamide	50-1500	1-2	5	Liver/kidney
Chlorpropamide	100-500	1	36	Kidney
Tolbutamide	500-3000	2-3	4	Liver
Second generation				

Glibenclamide	2.5-20	1-2	12	Liver/kidney
Gliclazide	40-320	1-2	10-12	Liver/kidney
Glipizide	2.5-30	1-2	3.5	Liver/kidney
Glyburide	1.25-220	1-2	12-14	Liver/kidney
Glimepiride	1-8	1	5-8	Liver/kidney

Special Features of Sulphonylureas

Less incidents of hypoglycaemia,drug interactions are observed with second generation drugs.

In patients with CKD preferred drugs are tolbutamide, tolazamide. MC side effect of Glibenclamide is hypoglycaemia.

Biguanides[33]

Metformin

The drug of choice preferred in overweight type 2 DM patients who fail to give any response to dietary modification and weight reduction.

Mechanism :

Major action is prevention of hepatic glucose output and also they improve utilisation of glucose in the peripheral tissues.

Special Features

It reduces blood glucose in the fasting state and maintains insulin loss by preserving islet cells and also modifies lipid values especially triglyceride and low density lipoprotein level

reduction. It is contraindicated if serum creatinine more than 1.5mg/dl, Cardiac failure,liver failure, hypoxia, metabolic acidosis. It does not cause hypoglycaemia.

AlphaGlucosidase inhibitors[32]

This group has acarbose, miglitol, voglibose. It is useful in postprandial hyperglycaemia.

Meglitinide

This group includes repaglinide,nateglinide.These drugs also act on ATP sensitive potassium channel to increase insulin secretion should be avoided in presence of lever disease.

Thiazolidinediones

Drugs include pioglitazone,rosiglitazone.

Mechanism in cells:

Pioglitazone binds to PPAR gamma.This promotes adipocyte differentiation & reduced insulin resistance in skeleton muscles.

Dose of pioglitazone is 15-45 mg/day.

It is contraindicated in liver disease & CCF. Rosiglitazone is associated with increased incidence of acute MI so it has been withdrawn from the market. Pioglitazone is associated with weight gain & rise in LDL level.

Incretin based therapy [47]

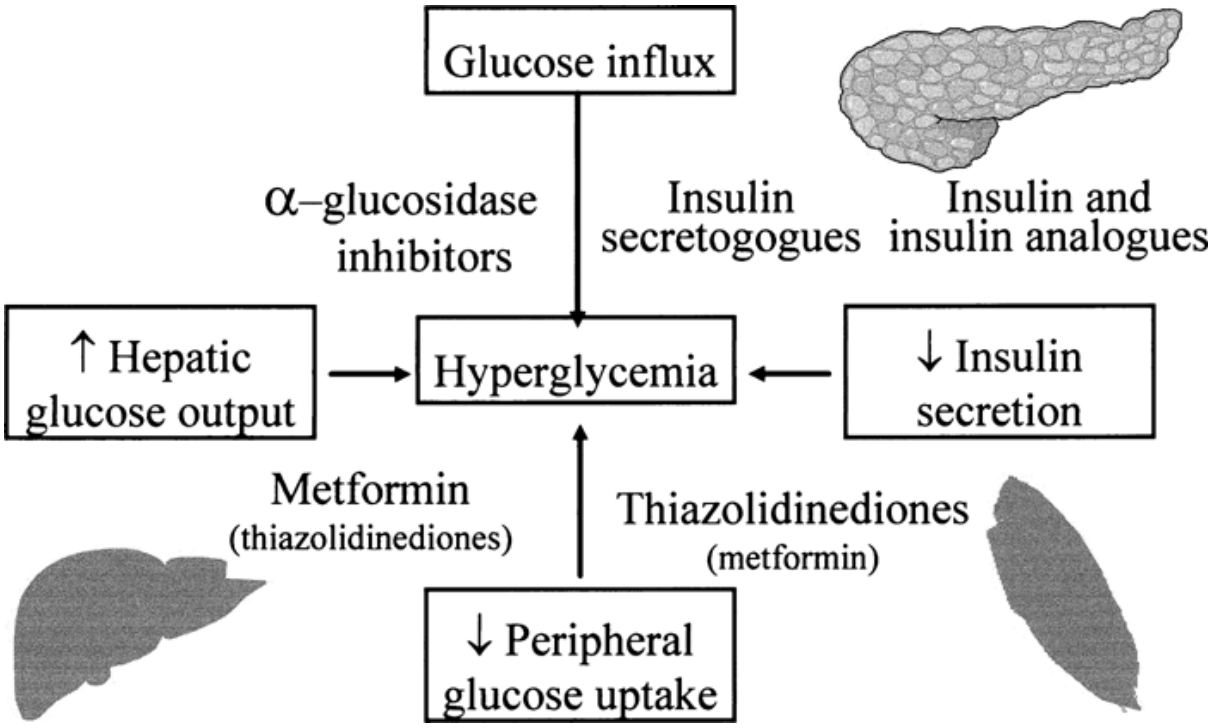
Glucagon like peptide [GLP-1]analogues are Exenatide, Liraglutide. They act on their receptors present on islet cells to stimulate insulin secretion in response to food. This potentiation of insulin secretion by the gut is referred to as the incretin Effect.

Dipeptidyl peptidase iv inhibitor[33]

1. Saxagliptin.

2. Sitagliptin.

3. Vildagliptin.



Insulin[50]

Class	Type	Peak effect(Hours)	Duration of Action(Hours)
Rapid	Regular(crystallline)	2-4	6-8
	Semilente	2-6	10-12
Intermediate	Isophane(NPH)	6-12	18-24
	Lente	6-12	18-24
Long acting	Protomine zinc	14-24	36
	Ultra lente	18-24	36

Insulin analogues[50]

Short acting:

1. Lispro
2. Aspart
3. Glulisine

Long acting:

1. Glargine
2. Detemir

Insulin Lispro

- Lispro insulin is produced by reversing aminoacid positions in 28 and 29 in the beta chain of insulin..

- It has a rapid on set of action (<15 mins),lowers glucose value with in 60 to 90 minutes
- Risk of hypoglycaemia is very low.
- Insulin Glargine
- Lispro is differentiated from human insulin by amino acid substitution of aspargine by glycine at 21st position in alpha chain and addition of two arginines to C-terminal of beta chain.

  Duration of action is upto 24 hours.

Insulin Detemir

- It combination with aspart will closely mimics normally insulin profile.

Insulin Regimens[50]

1. **Conventional insulin therapy.**

   In this therapy intermediating acting insulin or added to short doses of short acting insulin to achieve normal blood sugar status.

   SPLIT DOSE REGIMEN-two thirds of total dose is given before breakfast & the remaining one third before dinner.

2. **Multiple subcutaneous injections**

   First total dose of insulin is calculated as follows:

   0.6 –0.7 units/kg wt/day.

   25% of dose calculated by above formula is given at night as intermediate acting insulin.

   75% of calculated dose is given in three divided dose as regular insulin as follows.(40% of dose prior to break fast,30% prior to lunch,30% at dinner).

3. **Continuous infusion of subcutaneous insulin**

   Here a small pump is used which operates with the help of a battery.

It functions to release fasting and posprandial insulin insulin similar to normal physiological cycle.

About 45% total daily dose is given at basal rate, the reminder being administered as pre prandial boluses.

The dangerous complication of this regimen is nocturnal hypoglycaemia

Euglycaemic diabetic ketoacidosis is a rare interesting complication associated with this regimen

Indications For Insulin Therapy[18]

1) DM type one
2) Diabetic ketogenesis/acidosis
1) Non ketotic hperosmolar syndrome
2) Surgery,Infections,trauma
3) Pregnancy
4) Non obese Type-2 DM unresponsive to OHAs
5) Post renal transplantation diabetic patients

Complications associated with Insulin Therapy[50]

1) Hypoglycaemia
2) Reactions at the site of injection like itching , erythematous lesions and local indurations and nodules at the site of prick
3) Atrophy of fat or fat hyper trophy
4) Formation of anti-insulin antibodies

The goal of insulin therapy are

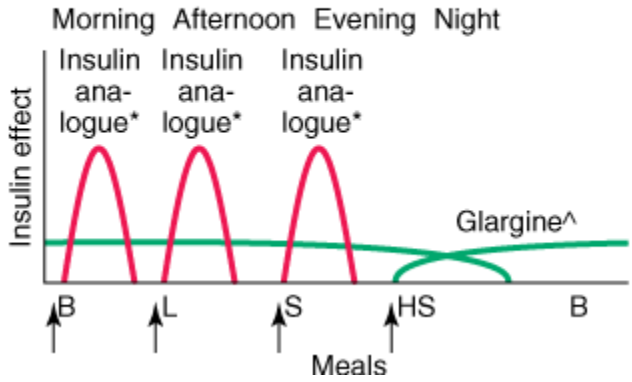
1) Normal growth & development children

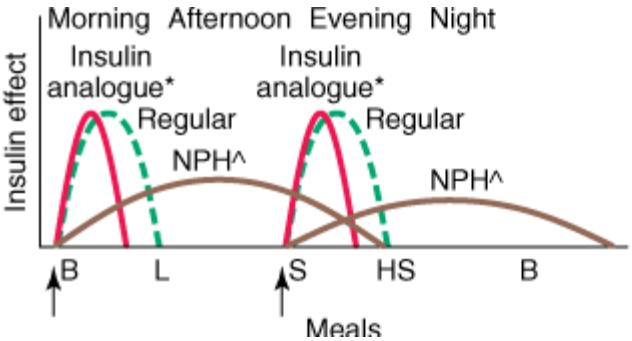
2) Prevention of complications

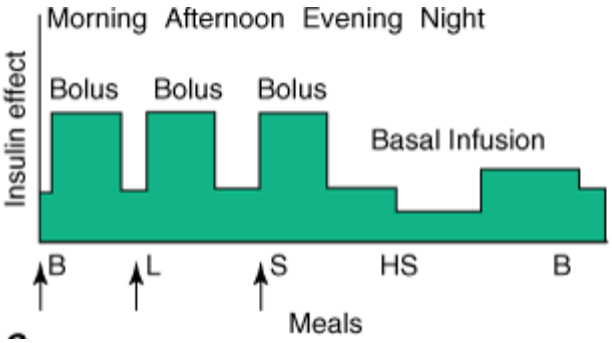
3) Normal pregnancy & delivery & conceptus in females

4) Acceptable glycaemic control with minimal hypoglycaemia

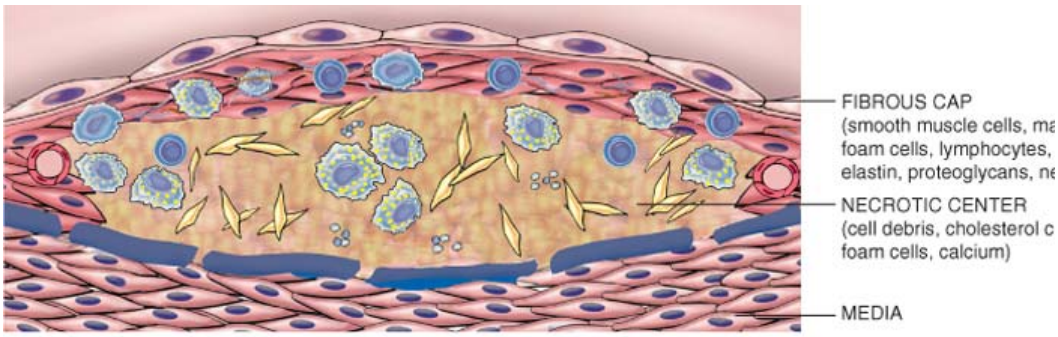
5) Minimal interference with psychological adjustment[18]







ATHEROSCLEROSIS



Atherosclerosis is defined pathologically by lesions with in the blood vessel called as atheromas (can also be defined as atherosclerotic plaques), that are visualised within the intimal layer of vessel. The atheromatous plaque or lesion is characterised by soft yellowish protruding structure of lipid core that is formed with the help of cholesterol and cholesterol esters that is further covered by a fibrous cap, which is firm and whitish.[1]

These atherosclerotic plaques obstructs the blood flow and reduces the strength of tunica media and it causes breakage of the vessel layer that results in sudden catastrophic thrombosis in the innermost layer. Atherosclerosis is the leading cause for increased number of casualties among the Indian people. The significant morbidity and mortality associated with carotid atherosclerotic disease, stroke.[1,2]

PRECIPITATING CAUSES AND RISKS FOR ATHEROSCLEROSIS[3]

Major risk factors (non modifiable)

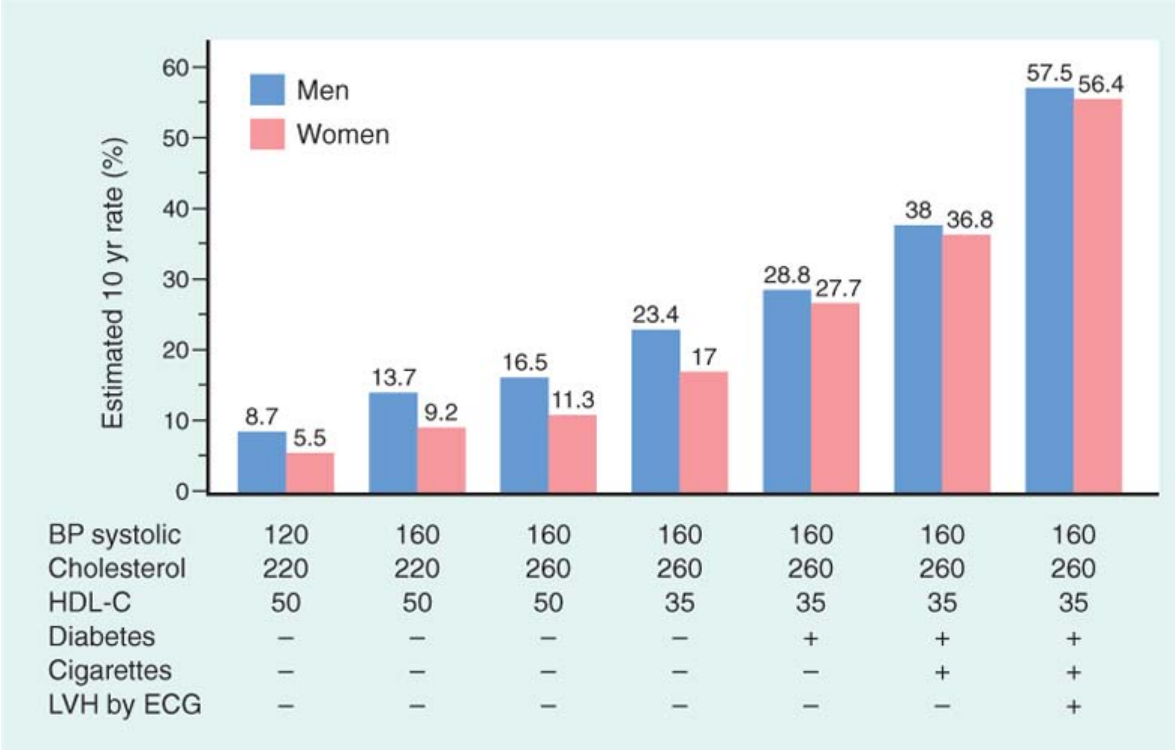
1) Advancing age
2) No Physical activity
3) Male sex
4) Stress ("type A personality)
5) Family history of atherosclerosis

6) Postmenopausal oestrogen deficiency
7) Genetic malformations

Modifiable risk factors

1) Hyperlipidemia
2) Type 2 diabetes mellitus
3) Hypertension
4) Infection due to Chlamydia Pneumoniae
5) smoking
6) C-reactive protein
7) Excess intake of carbohydrate
8) Altered Lipoprotein(a) levels
9) ***Excess*** (trans)unsaturated fat intake

An important factor influencing atherosclerosis is age .When atherosclerotic lesions clinically manifest, the lesions had reached a critical threshold. In men, the incidence of myocardial infarction increases 5 fold, between ages 40 and 60. Before the clinical features occur, the arterial lesions will evolve beforehand. [3]



Because of the hormonal support of oestrogen and progesterone the premenopausal women are protected from risk of coronary artery disease. At the same instant, the postmenopausal women are predisposed to diabetes, hyperlipidemia, or severe hypertension. Myocardial remodelling, infarct healing, and haemostasis are also influenced by female sex.

The atherosclerosis and IHD has a multi factorial causation .[3]

Major Modifiable Risk Factors for IHD

Hyperlipidemia

Hypercholesterolemia is considered as a single most risk factor for atherosclerosis, because it independently accelerates the risk for heart disease without the presence of other risk factors. Low-density lipoprotein (LDL) cholesterol is the main determinant of atherosclerosis and coronary artery disease. [3]

The reverse cholesterol transport is mediated by HDL cholesterol (it moves cholesterol from organising inside atheromas and shifts the cholesterol particles into liver such that it gets into the bile for excretion process). The reduced risk of IHD is observed in individuals with high level of HDL cholesterol.[2,3]

Hypertension

In a normotensive individuals there is 60% reduction in the incidence of IHD compared to hypertensive individuals. The influence of both diastolic and systolic BP is equally important in predisposing CAD.The major leading cause of cause of death in hypertensive patients are CCF ,IHD and stroke.In chronic hypertensive individuals, Left ventricular hypertrophy is predominantly seen.

Cigarette Smoking [3]

The incidence of IHD is increased by 200%in cigarette smokers compared to non-smokers.

Diabetes mellitus is the single most important determinant of atherosclerosis compared to non diabetic individual. Hyperglycaemia directly predispose to hypercholesterolemia.

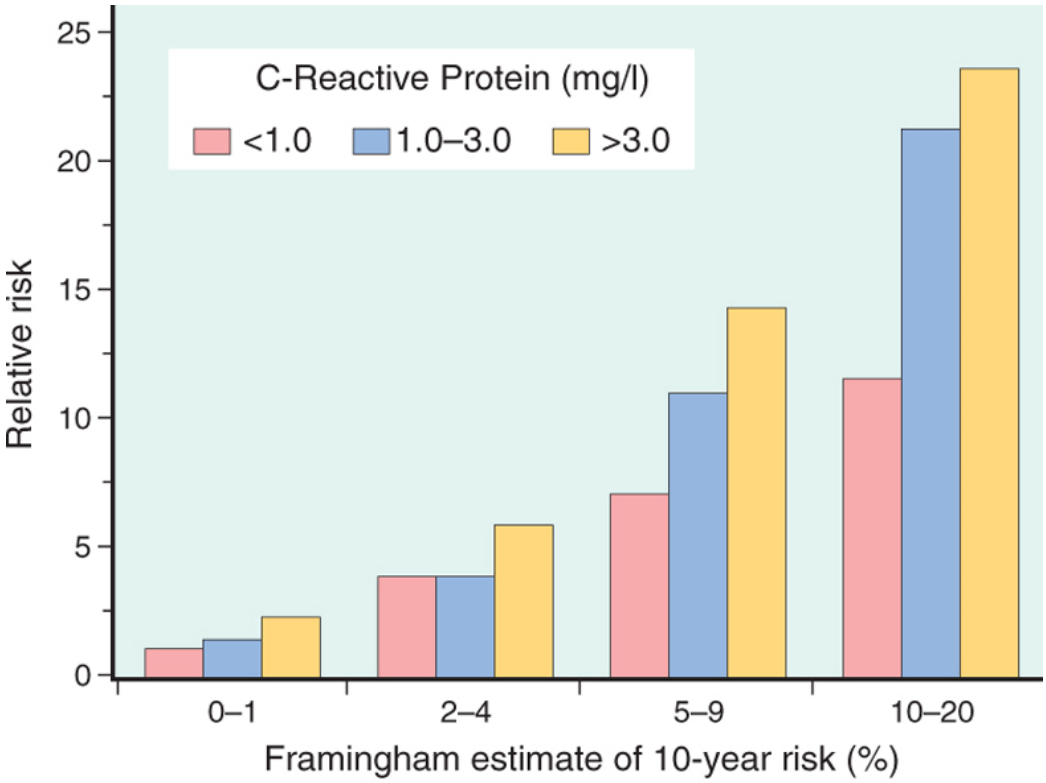
Role of C-reactive protein [14]

Atherosclerosis can be considered as a inflammatory process .High levels of circulatory inflammatory markers observed during the phases of plaque formation and rupture.

C Reactive protein plays a central role in atherosclerosis by mediating local endothelial adhesion and thrombotic state. Peripheral arterial disease, Stroke, myocardial infarction, and sudden cardiac death are seen in individuals with increased levels of CRP in the serum.

Hyperhomocystinemia[3]

Also a risk factor for atherosclerosis



Stroke, coronary artery disease, peripheral vascular disease, , and venous thrombosis are associated with increased level of serum homocystine. Accelerated atherosclerosis is observed in individuals with increased homocystine level of more than 100 µmol/l. Hypovitaminosis B and folic acid deficiency are associated with elevated homocystine levels.

Atherosclerosis and Lipoprotein (a)[13]

Lipoprotein a, short named as Lp(a), is a modified LDL . In CAD and CVA raised levels of lipoprotein[a] is an important risk factor.

Factors Affecting Haemostasis

Increased levels of plasminogen activator inhibitors are found to have an increased risk of acute myocardial infarction and cerebrovascular accidents.

Use of COX-2 inhibitors leads to suppression of endothelium-derived prostacyclin without affecting platelet-derived factor thromboxane A2, hence producing a prothrombotic state that increases the risk of ischemic events.

Other Factors

Lack of exercise, "type A" personality and obesity

Pathogenesis[4,5]

Chronic endothelial injury

Increased permeability and leukocyte adhesion, thrombosis

Oxidised of form of LDL accumulation in the vessel wall

Migration into intima

Transformation into macrophages

Secretion of platelet activating factor from macrophage

SMC recruitment from media

ECM deposition both extracellularly and intravascularly

Gives rise to fatty streaks

On further evolution,fibrofatty atheroma

Proliferated SMC, foam cells, extracellular lipid, and ECM are the major constituents of fibro fatty atheroma.

Interaction of modified lipoproteins,T lymphocytes ,macrophage,Chronic or repetitive endothelial injury are the basis for atherosclerosis.

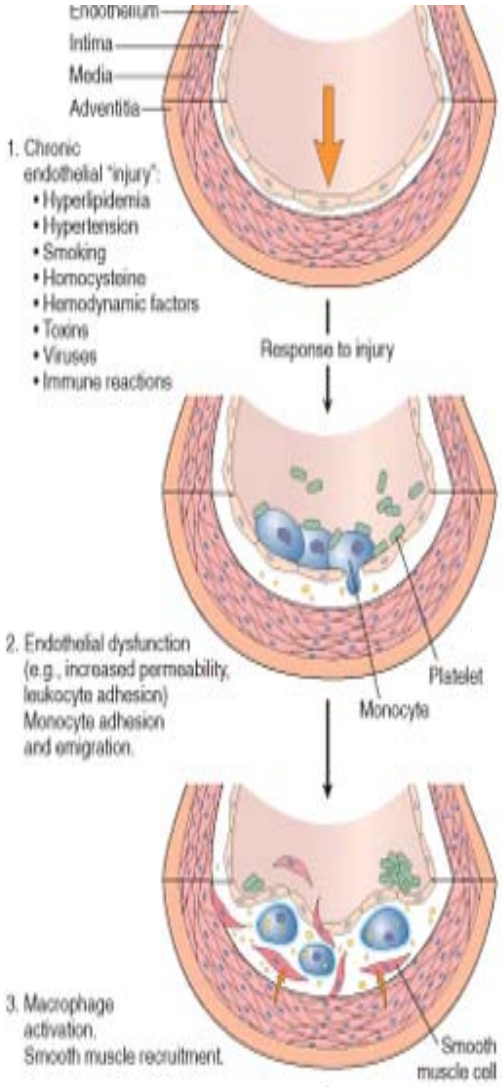
Initial lesions starts at sites of normally intact endothelium within which there occurs increased tendency of endothelial permeability ,thereby enhancing leukocytic cell adhesion, and this is furher complicated by altered genetic expression.[13]

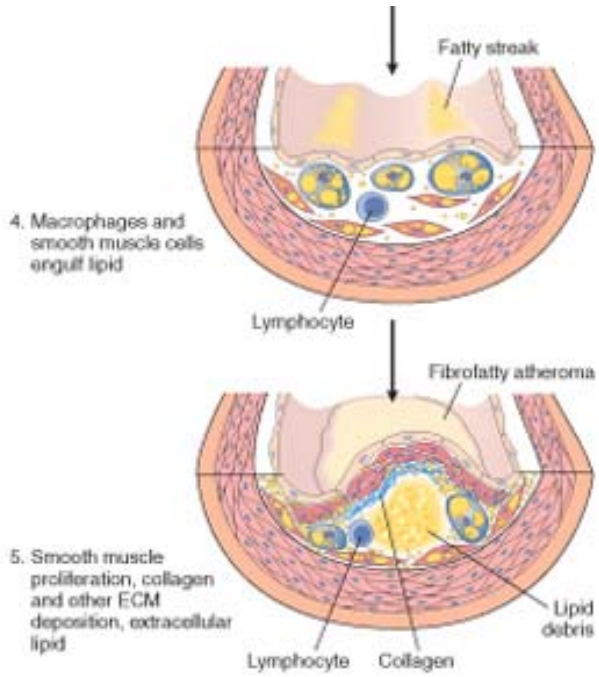
An important etiological risk for endothelial dysfunction is hemodynamic disturbances and hypercholesterolemia. Inflammation is also an important cofactor. Other causes like cigarette smoking, hyper homocysteinemia and also exposure to infectious agents had contributed to it.

Virchows triad includes endothelial injury, vascular stasis and hypercoagulability. Injured endothelium causes release of procoagulant factors,

Imbalance between pro coagulant and anti coagulant factors plays an important role. soon after endothelial injury there is reduced production of PGI2 ,thrombomodulin and enhanced production of PAIs.

Thereby the triad forms an important contributing factor for atherosclerosis[5]





Plaque commonly occur at the origin of exiting vessels, at points where they divide, and also alongside the dorsal wall of the abdominal aorta due to alteration in the flow patterns in these areas.[4]

Non turbulent laminar flow that is present in other normal vessels is actually protective against atherosclerosis due to liberation of superoxide dismutase.

Lipids

Lipids substances generally move in the bloodstream via attachment to specific apoprotein receptors.

Dyslipoproteinemias include (1) Excess level of LDL cholesterol (2) decreased amount of HDL , and (3) excess levels of mutated Lipoprotein(a) 4)nephrotic syndrome, alcoholism and hypothyroidism[15]

The following description gives the role of cholesterol in the atherosclerotic process:

- Cholesterol and cholesterol esters are commonly found in atheromatous plaques. Accelerated atherosclerosis in homozygous familial

hypercholesterolemia may lead to defective LDL receptors and inadequate hepatic LDL uptake which in turn can lead to myocardial infarction before the age of 20 years.

- Premature atherosclerosis is commonly seen in diabetes and hypothyroidism .There is significant correlation between the severity of atherosclerosis and the levels of total plasma cholesterol or LDL.
- Drugs that reduce the levels of serum cholesterol slows the rate of progression of atherosclerosis, and reduces the risk of cardiovascular events.

The process by which excess lipidemia contributes to formation of atheromatous lesion is described as follows:[5,15]

Chronic hyperlipidemia

Accumulation of reactive oxygen species,local shear stress

Formation of oxidised LDL

Endocytosis of oxidised LDL through scavenger receptors into the macrophages

Liberation of inflammatory cytokines (TNF-alpha,IL-1,TGF-beta)by activated macrophages

ECM deposition, fibrofatty streak leads to Inflammation.

In early stages of atherogenesis there occurs an alteration in the extracellular expression of adhesion molecules - vascular cell adhesion molecule which binds to T lymphocyte cells and monocytes.

Activated macrophages produce reactive oxygen species, aggravating LDL oxidation.T lymphocytes recruited to the intima, interact with macrophages and can generate a chronic immune inflammatory state.[15,4]

Infection

Infections may be associated with the local inflammatory process that results in atherosclerotic plaque, Herpesvirus, cytomegalovirus, and Chlamydia pneumoniae have been frequently observed in atherosclerotic plaque.[2,5]

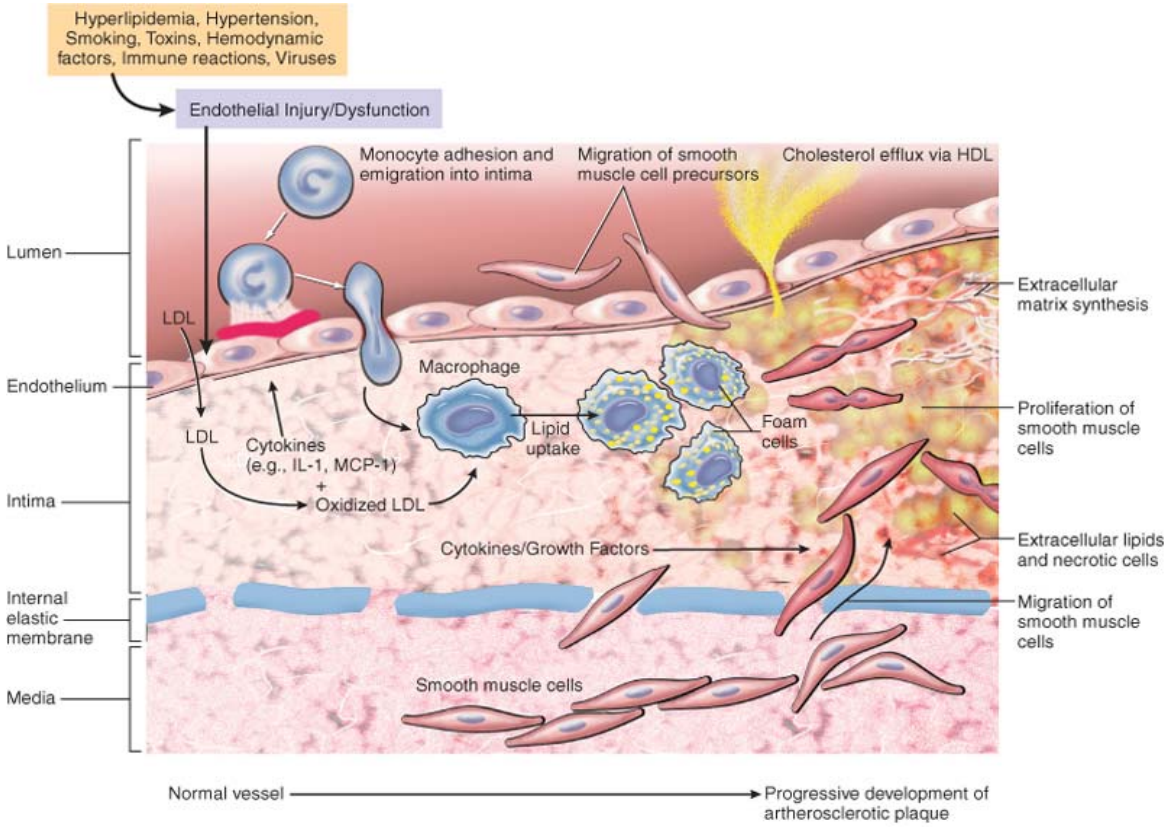
Sero epidemiologic studies have found an elevated antibody titers for*C. pneumoniae* in subjects who were found to have severe atherosclerosis.

Smooth muscle cell proliferation and its deposition in the extra cellular matrix converts the existing fatty streak into a mature atheromatous structure and this contributes to the gradual growth of atherosclerotic plaques.[7,8]

Some growth factors contribute in Smooth muscle proliferation and Extracellular matrix depositions which includes fibroblast growth factor, transforming growth factor beta and platelet derived growth factor.

The recruited Smooth muscle cells manufacture Extracellular matrix which strengthens and hardens the atherosclerotic plaques.

Activated mononuclear cells in atherosclerotic areas causes Smooth muscle cell apoptosis in the blood vessel, increased catabolism of ECM, resulting in formation of highly unstable lipid plaques.



Morphology[6]

Fatty Streaks. Fatty streaks are composed of lipid-filled foam cells.It usually do not cause any disturbance in blood flow. Initially they can be observed as multiple minute yellow, flat spots that can coalesce into elongated streaks, 1 cm long. Coronary fatty streaks begin to form in adolescence, at the same anatomic sites that tend to develop into plaques later. The relationship of fatty streaks to atherosclerotic plaques is uncertain; although they may evolve into precursors of plaques.

Atherosclerotic Plaque. The key processes in atherosclerosis are intimal thickening and lipid accumulation. Plaques vary from 0.3 to 1.5 cm in diameter.

Atherosclerotic lesions are patchy, commonly involving only a portion of any given arterial wall. On cross-section, the lesions appear eccentric. The focality of atherosclerotic lesions is almost certainly due to the variations in vascular hemodynamics. Certain portions of a vessel wall are more prone to plaque formation due to disturbance in vascular flow.

Smooth Muscle Proliferation

Smooth muscle cell proliferation and its deposition in the extra cellular matrix converts the existing fatty streak into a mature atheromatous structure and this contributes to the gradual growth of atherosclerotic plaques. Some growth factors contribute in Smooth muscle proliferation and Extracellular matrix depositions which includes fibroblast growth factor, transforming growth factor beta and platelet derived growth factor.

The recruited Smooth muscle cells manufacture Extracellular matrix which strengthens and hardens the atherosclerotic plaques.

Activated mononuclear cells in atherosclerotic areas cause Smooth muscle cell apoptosis in the blood vessel, increased catabolism of ECM, resulting in formation of highly unstable lipid plaques.

ORDER OF INVOLVEMENT OF VESSELS:[13]

1Lower abdominal aorta

2.Coronary arteries

3.Popiliteal arteries

4**.**Internal carotid arteries

5.Circle of willis

Arteries of the upper limb, the mesenteric and renal arteries are usually spared.

Principal components of atherosclerotic plaque include[6]

(1) Cells including activated macrophages, T lymphocyte cells and smooth muscle cell.

(2) Lipid moiety present both intra and extracellularly

(3) Elastic fibers, collagen tissue and proteoglycans

The **fibrous cap present in the outer part** is composed of Smooth muscle cells and dense collagenous tissue. Underlying the "**shoulder**" is a complex cellular area containing activated macrophages, T cells, and Smooth muscle cells.

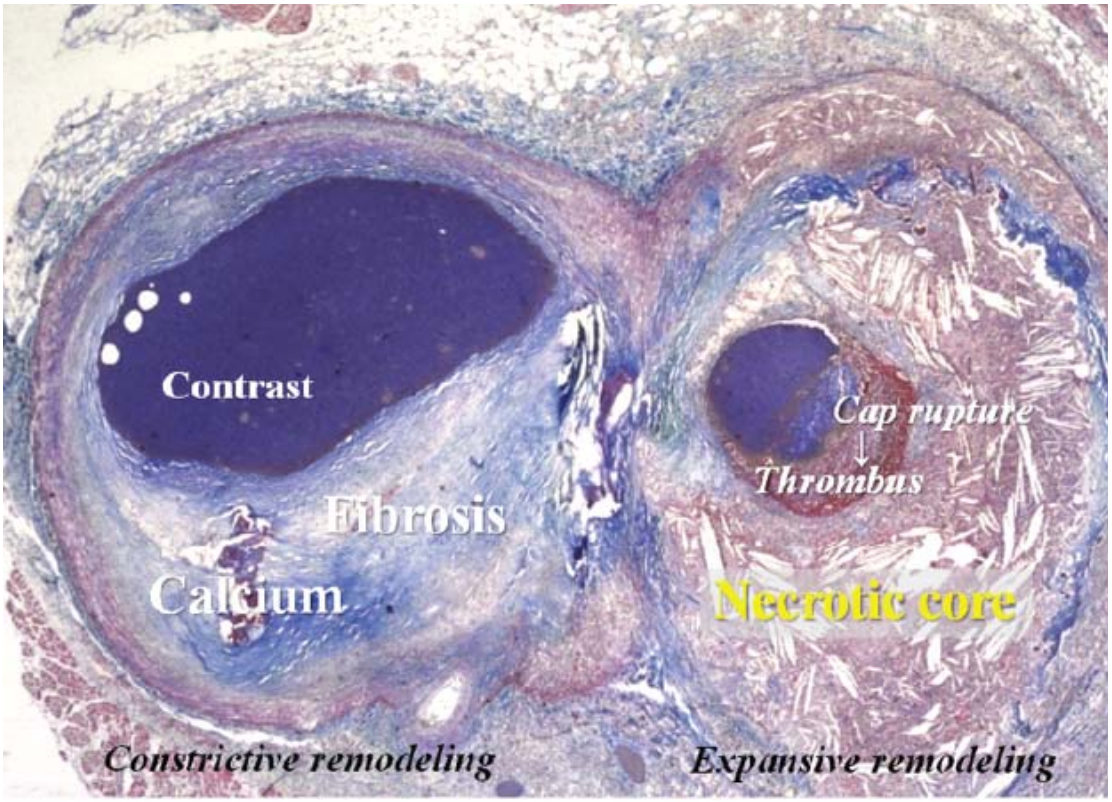
Deeper parts of fibrous cap contains a **necrotic core**, that has lipid debris from dead cells, foam cells, fibrin, variably organized thrombus. In the border of lesions, there is a zone of **neovascularization** (growing new tiny blood vessels). Normal atheromas have abundant lipid in them.

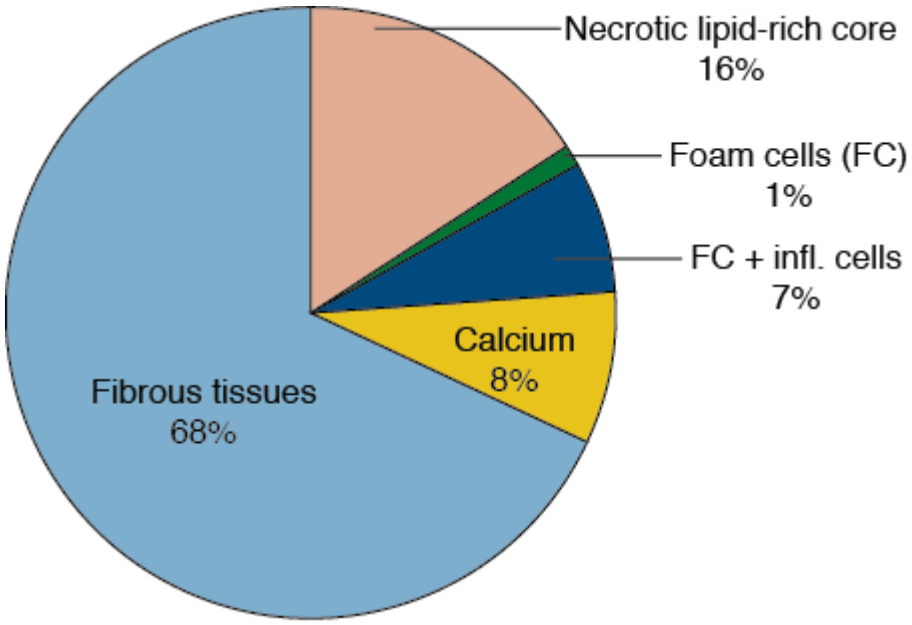
Plaques evolve through variable degree of cell destruction, degeneration, replication and remodelling of Extracellular marix layer , and stabilisation of thrombi. This atheroma undergo **calcification inside.** People with advanced calcification in the coronary arteries are highly succeptible for coronary events in the future.[11]

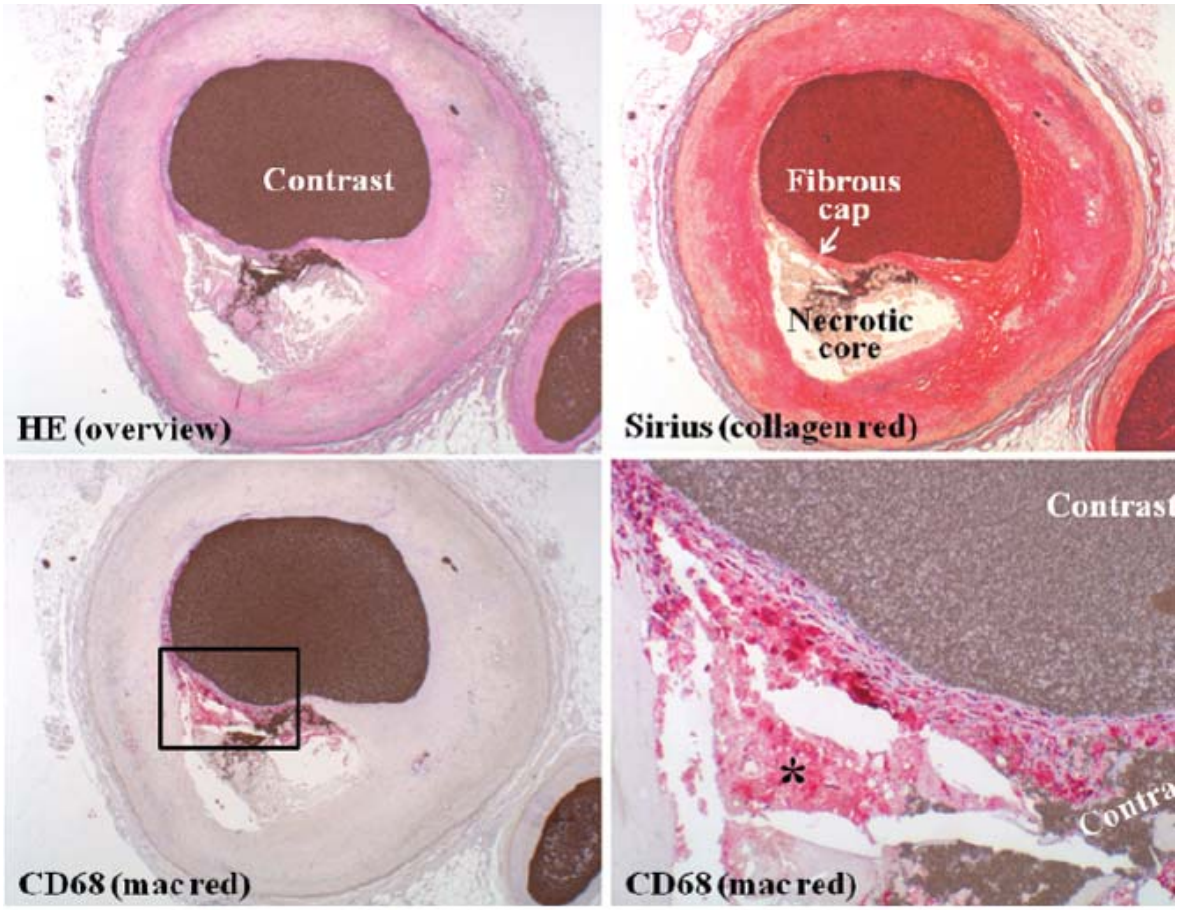
Acute atheromatous plaque changes like **Rupture, ulceration, or erosion** of the luminal surface of atheromatous plaques makes the bloodstream viable to highly thrombogenic,substances and induces thrombus formation leads to downstream ischemia.

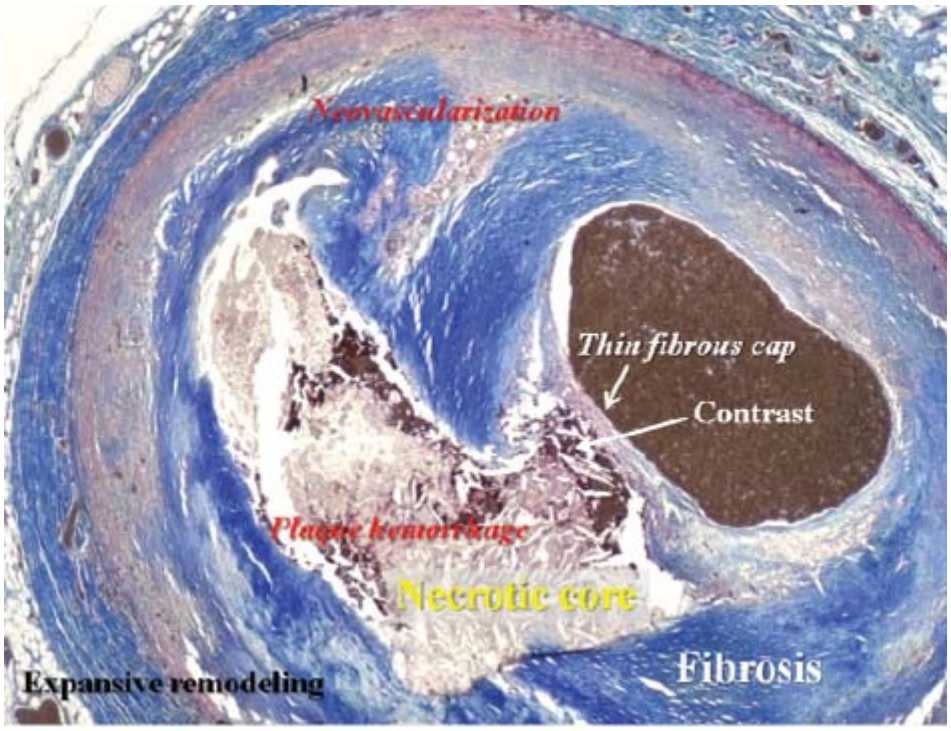
Rupture of the overlying fibrous cap or of the thin-walled vessels in the areas of neovascularization can lead to intra-plaque hemorrhage.[11]

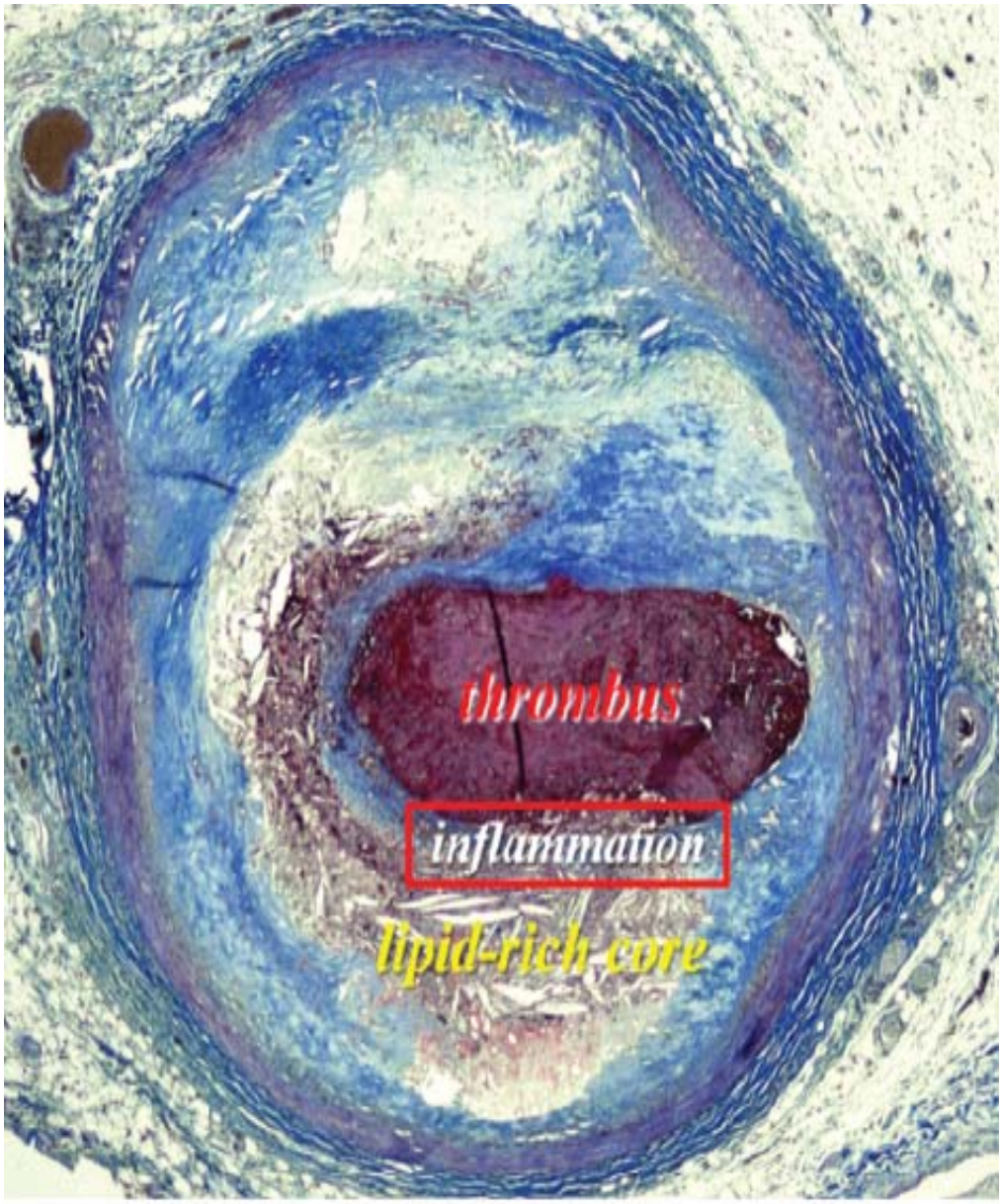
Plaque rupture can discharge debris into the bloodstream, producing microemboli. Aneurysms are usually caused by weakening of vascular intima in atherosclerosis.

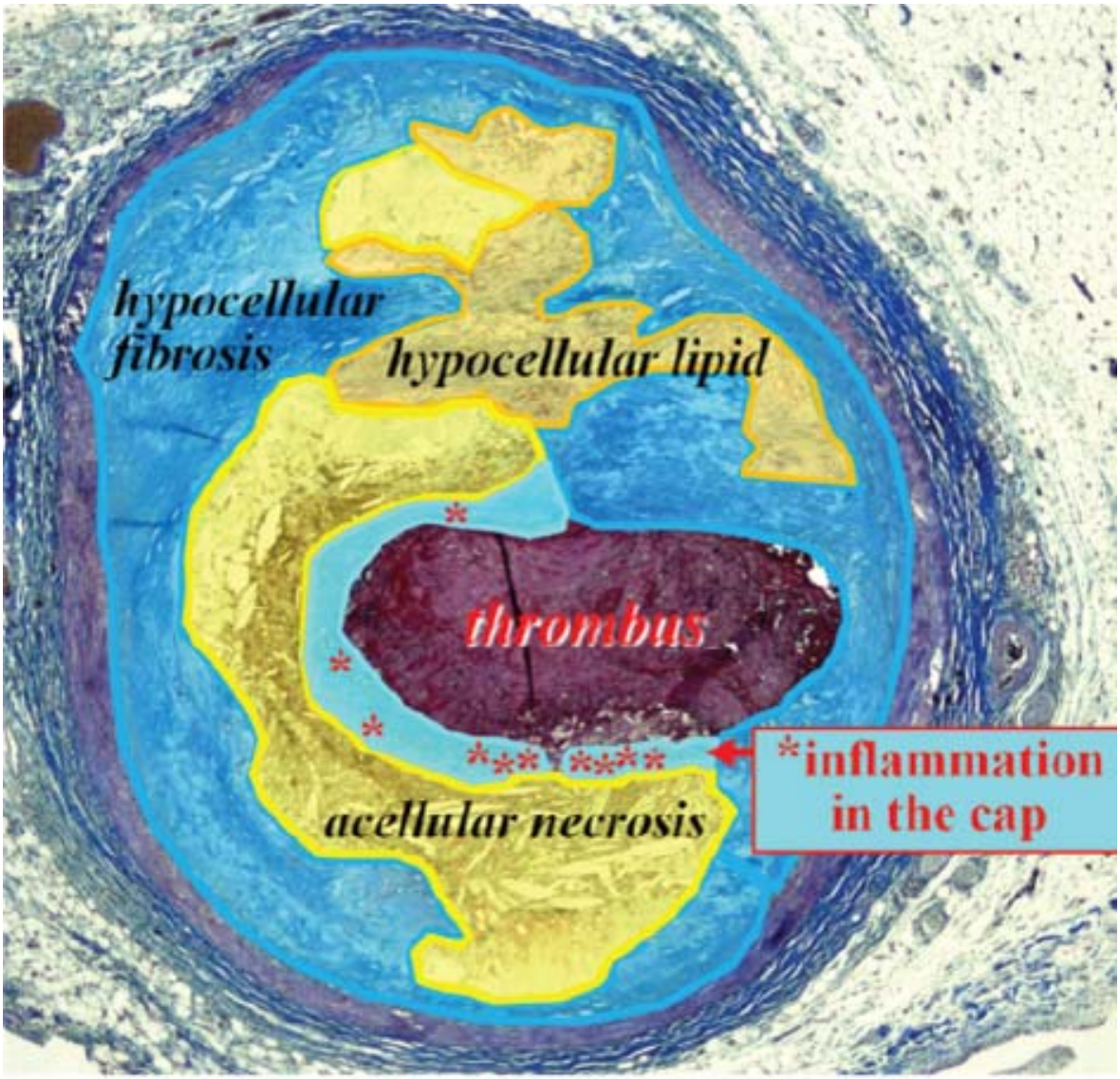

Contrast
Fibrosis
Calcium
Cap rupture
Thrombus
Necrotic core
Constrictive remodeling
Expansive remodeling

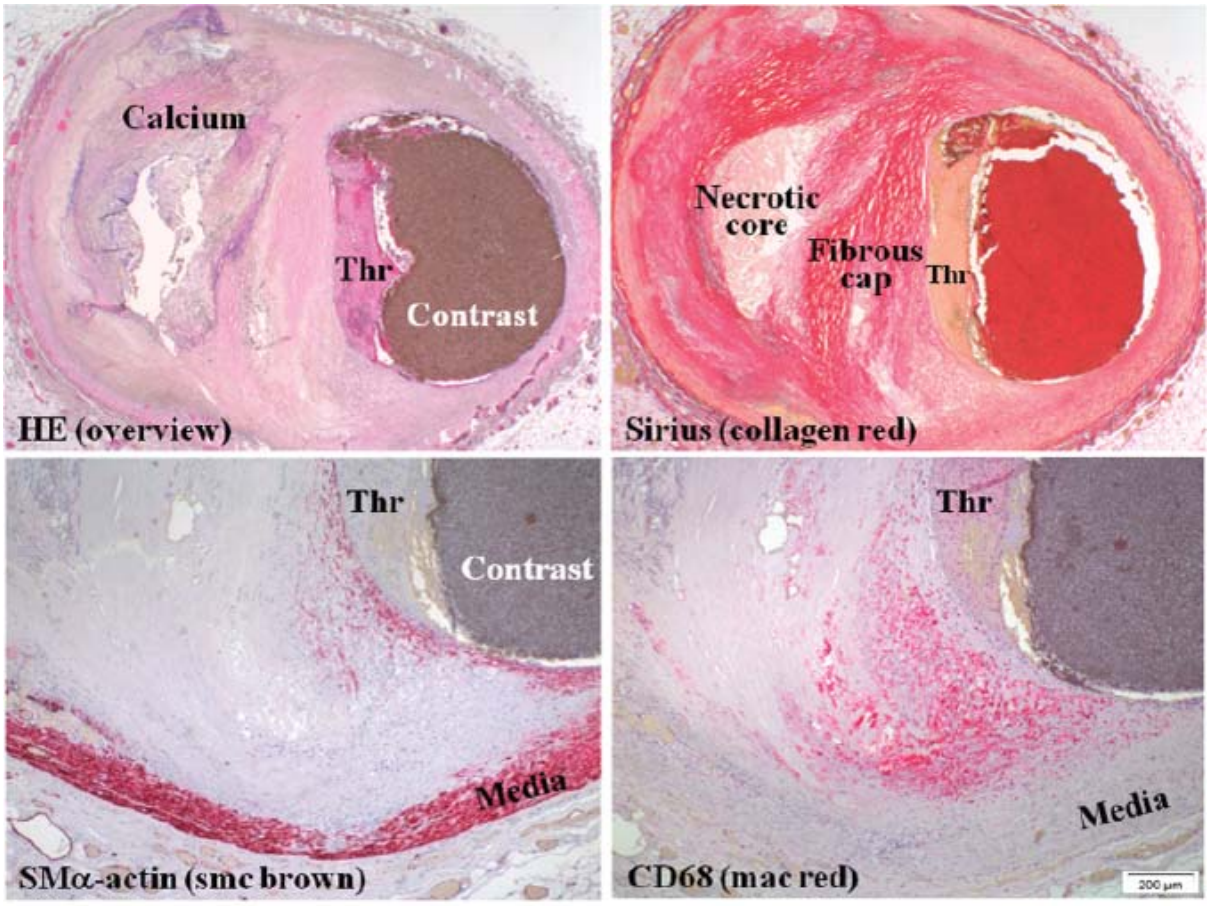

Necrotic lipid-rich core
16%
Foam cells (FC)
1%
FC + infl. cells
7%
Calcium
8%
Fibrous tissues
68%

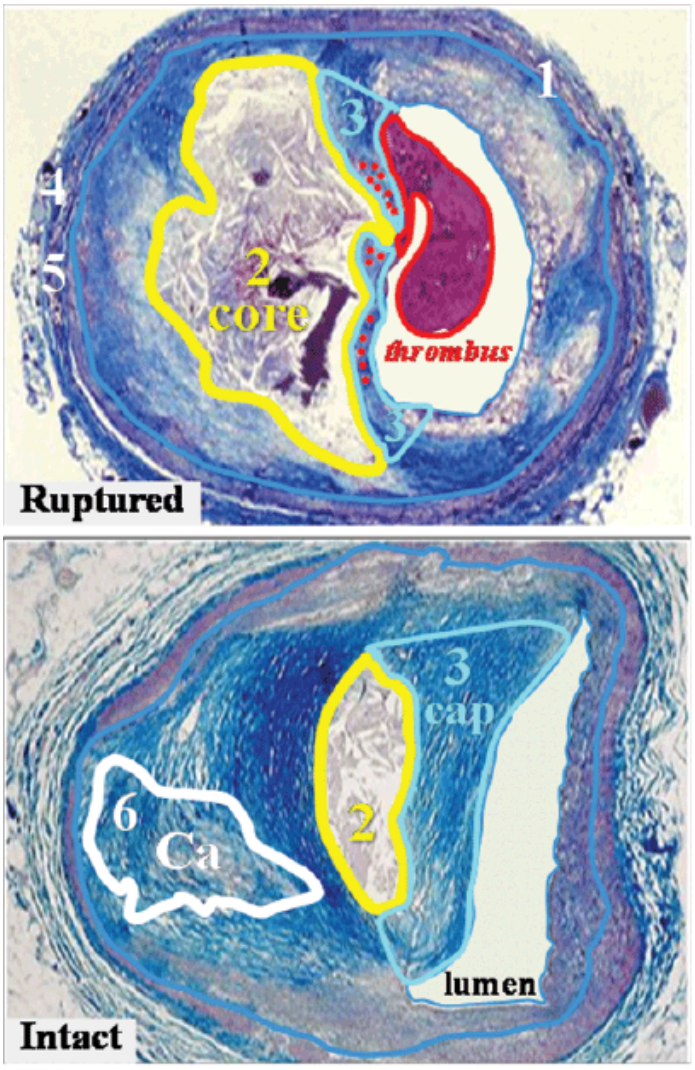

Contrast
HE (overview)
Fibrous cap
Necrotic core
Sirius (collagen red)
CD68 (mac red)
Contrast
*
CD68 (mac red)


Neovascularization
Thin fibrous cap
Contrast
Plaque hemorrhage
Necrotic core
Fibrosis
Expansive remodeling


thrombus
inflammation
lipid-rich core


hypocellular fibrosis
hypocellular lipid
thrombus
acellular necrosis
*inflammation in the cap


Calcium
Thr
Contrast
HE (overview)
Necrotic core
Fibrous cap
Thr
Sirius (collagen red)
Thr
Contrast
Media
SMα-actin (smc brown)
Thr
Media
CD68 (mac red)
200 µm



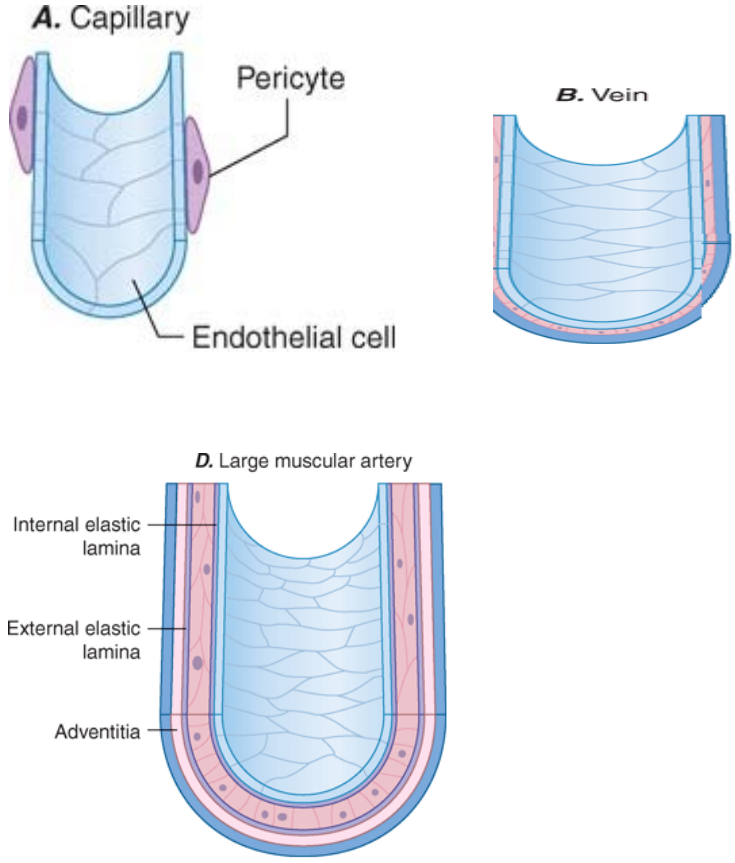
Natural History of lipemic sclerosis [[13,5]

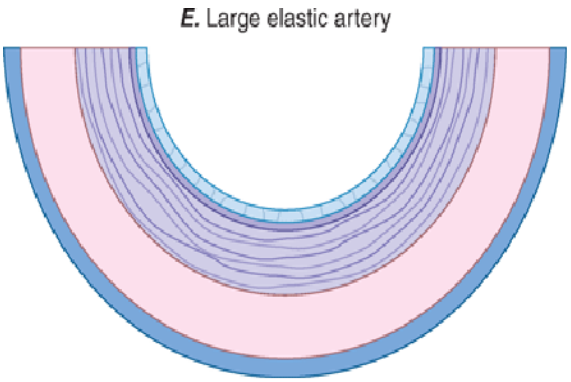
The process commonly affects major elastic arteries like aorta and its branches, carotid artery, large and medium sized muscular arteries like the major coronary arteries and its branches. In major arteries, plaques are degenerative, that involves the adjacent media and weakens the involved vessel wall, that forms aneurysms which later can rupture.

Events occurring are

- Increased arachidonic acid metabolism
- Increased thromboxane A_2 synthesis
- Decreased nitric oxide and prostacyclin production

- Decreased antioxidant levels
- Increased expression of activation-dependent adhesion molecules (e.g., glycoprotein IIb/IIIa, P-selectin)
- Increased platelet microparticle formation
- Increased platelet turnover
- Reduced membrane fluidity.[5]





NORMAL CAROTID WALL

STRUCTURE

The walls of all arteries consist of three distinct layers. The deepest layer is called as tunica intima, or also defined as epithelial lining .The layer next to T.intima is T. media or otherwise called muscular layer.

This part of the vessel is responsible for strength,stiffness and elasticity of the artery. The superficial most layer is Tunica adventitia, which has loose connective tissue cells in them.

The tunica intima and the outer adventitia present as similar straight echogenic lines, interposed with an intersecting echo window that marks the T.media. Intimal reflection is normally thin straight and parallel to outer adventitial layer.[61]

Plaque deposition is evidenced by undulation and thickening. Fibromuscular hyperplasia will also causes undulation and thickening.

After endarterectomy, the intimal reflection that is normally seen will be absent at the site of surgery.

Since intimal layer is removed along with the atheromatous plaque, the neointima that covers the endarterectomy site is not visible sonographically.

The intimal reflection when seen in the longitudinal images the image plane will pass via long axis of the blood vessel.

In transverse sections, when the intima is seen, the image plane will be visualised perpendicular to the long axis of the blood vessel.

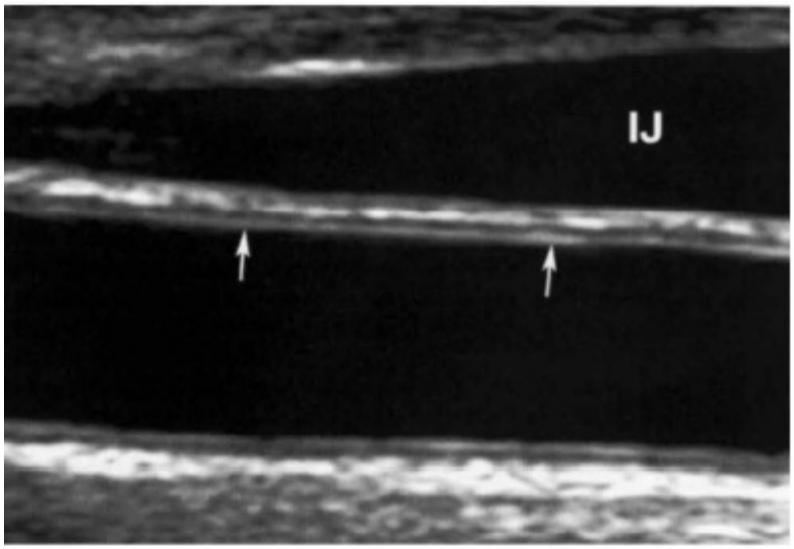
Pseudo thickening of artery may occur with off-axis longitudinal Images.

In normal arteries blood flow is laminar.

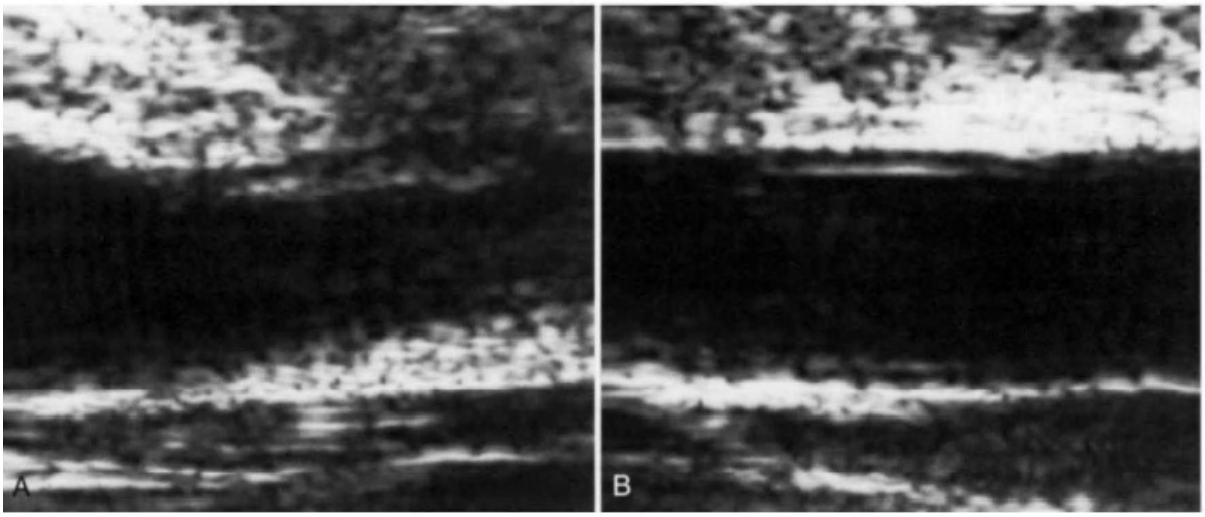
The disturbance in laminar flow was found to be in branching or tortuosity of the vessel wall.[64]

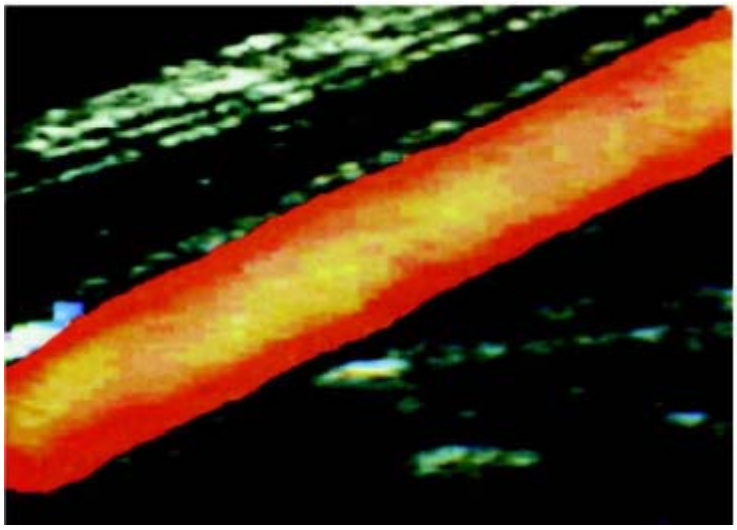
Table 7–1. Features That Identify the External and Internal Carotid Arteries

	Carotid Arteries	
Features	***External***	***Internal***
Size	Usually smaller	Usually larger
Branches	Yes	No
Orientation	Proceeds anteriorly, toward the face	Proceeds posteriorly, toward the mastoid process
Doppler characteristics	High-resistance flow pattern	Low-resistance flow pattern
Temporal artery tap	Waveform deflections	No deflections

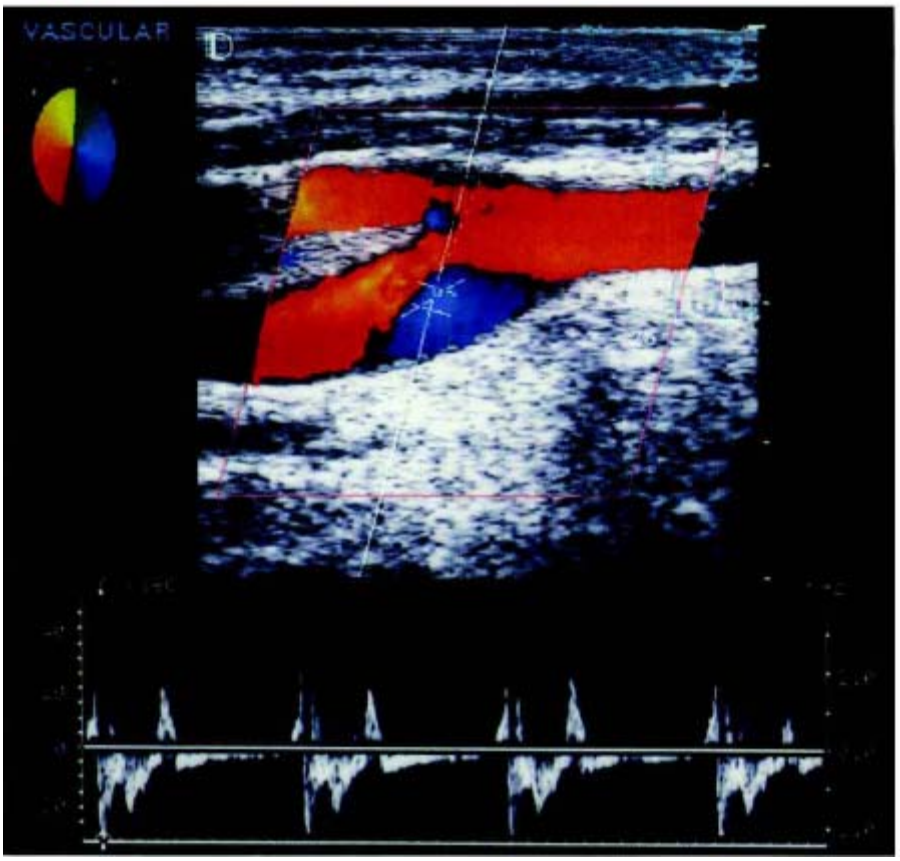


NORMAL ANATOMY OF THE COMMON CAROTID ARTERY.





Above diagram describes laminar flow pattern in the blood vessel. The darker peripheral area shows reduced flow motion at the corner of the blood part. The lighter area present throughout the blood vessel represents faster blood flow.[59]



The above diagram shows long axis view of carotid bifurcation. Blue area shown in the elongated part of the ICA represents normal reversed flow area (zone).[57]

EXAMINATION PROTOCOL[55,64]

INSTRUMENTATION

(1) High-frequency transducers that has small focal distances were used for near field work;

(2) Colour flow views;

(3) Pulsed, directional Doppler, having velocity measurement capabilities;

(4) Frequency spectrum analysis.

PATIENT POSITION

Carotid arteries are examined with patient lying flat in the bed with examiner sitting near the head end of the bed.

In order to expose the area of imaging for a wider part, same side shoulder is depressed to the maximum possible extent.

TRANSDUCER POSITION

Carotid bifurcation and internal carotid arteries are best approached in lateral and posterolateral view.

CAROTID ARTERY VERSUS JUGULAR VEIN

Normally flow in the carotid is towards the head and is pulsatile in nature with high velocity. But in jugular vein the flow pattern is towards the feet,it is non pulsatile, flow has a non oscillating uniform pattern and gives a sound of wind storm.

Jugular vein is thin when compared to carotid artery and it collapses when it is compressed with the probe. But carotid artery is thick and it gives a reflection from the inner layers.[63,59]

IMAGE ORIENTATION[64]

Longitudinal images are oriented in such a way that patients head is turned towards the left side.

Transverse images generally are depicted in such a way that it is seen from the foot end of the paient, with patients right half is towards left part of the image.

EXAMINATION SEQUENCE[55]

STEP 1.Choose the transducer position in postero lateral direction so that it displays the longitudinal view of the carotid vessel.

STEP 2.The peak systolic velocity is accurately measured with Doppler angle[60-70degree]

STEP 3.Colour flow imaging is used to survey the carotid bifurcation.The longitudinal images taken, begin at the clavicle proceeds to carotid bifurcation from there continue into ECA and ICA. The process is repeated with transverse images.

STEP 4. ICA and ECA are identified by spectral signals.

STEP 5.After the survey is completed the images transverse to the vessel axis are needed for the assessment of plaque thickness and lumen narrowing.[55]

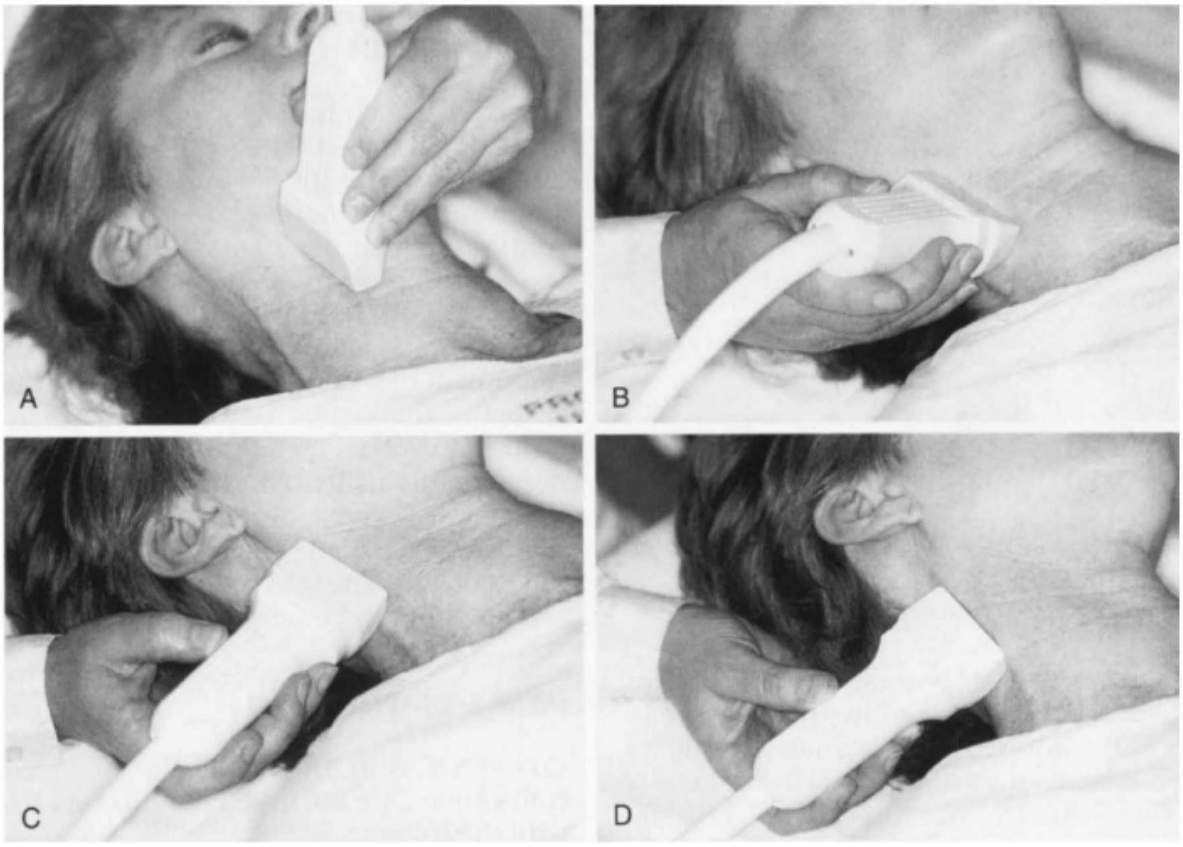
STEP 6.Angle corrected velocity spectra record when a stenosis is present. Plaque features are better shown in gray scale images than colour flow images.

STEP 7.Inter transverse segment of each vertebral artery is imaged and recorded.

STEP 8.Subclavian artery is assessed to detect stenoses and occlusion.

A Supraclavicular approach or transpectoral approach is used to image each subclavian artery from a long axis perspective.

By colour flow images we can determine location and length of stenosis and post stenotic flow disturbances [55,64].



VISIBLE BRUIT[61]

The visible bruit seen in colour flow images. A combination of colours is seen in the soft tissues near the blood vessel due to vibrations from the vessel wall and from the surrounding soft tissue. More vibrations from the vessel lumen indicate flow disturbance in the vessel.

The visible bruit is seen in

1. AV FISTULA

2. Arterial stenosis

3. Pseudo aneurysms

Color Flow Imaging -- principles

Colour flow images are obtained using

1. Time domain image

2. Colour Doppler

3. Power doppler

DOPPLER ULTRASOUND[62]

The Doppler Effect is a change in the frequency of detected wave when the source of the detector is moving. In medical ultrasonography, a Doppler shift occurs when reflectors move relative to the transducer. The frequency of echo signals from moving reflectors is higher or lower than the frequency transmitted by the transducer, depending on whether the motion is toward shift frequency, or simply the Doppler frequency,it is the difference between the received and transmitted frequencies.

POISEUILLES EQUATION

$$Q = \frac{\pi(P_1 - P_2)r^4}{8L\eta}$$

$$\frac{8L\eta}{\pi r^4} = \frac{P_1 - P_2}{Q}$$

$$R = \frac{8L\eta}{\pi r^4}$$

$$R = \frac{P_1 - P_2}{Q}$$

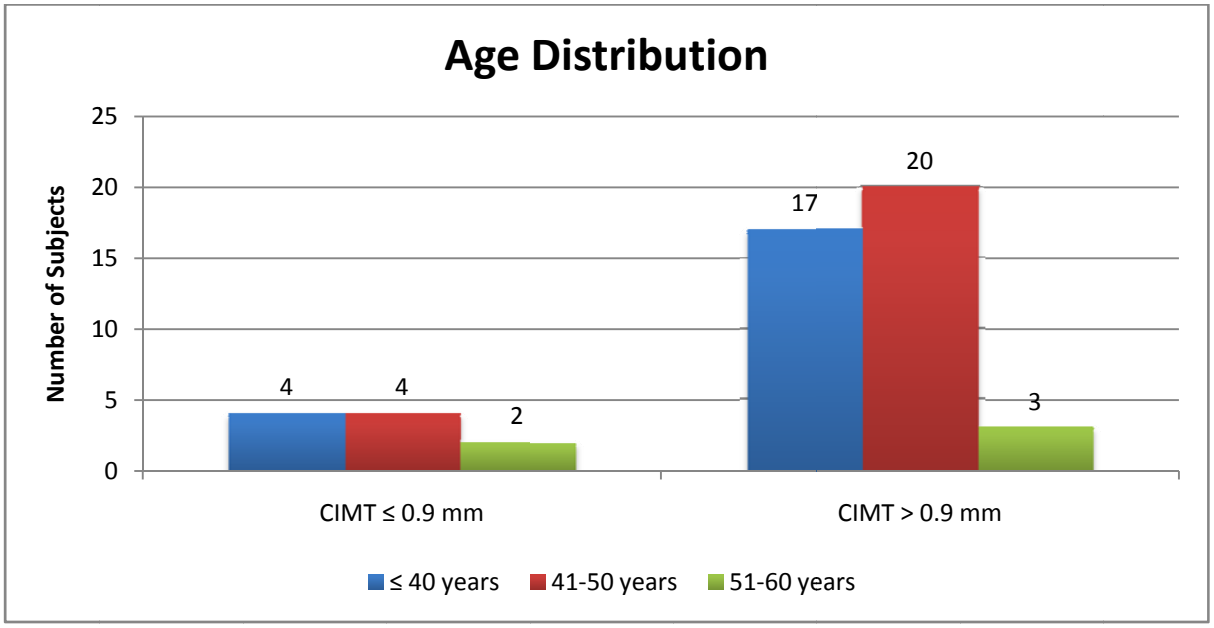
REYNOLD'S NUMBER

The factors that affect the development of turbulence are expressed by the dimensionless Reynold's number Re = vq2r/ŋ

Data Analysis

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test.. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

Age

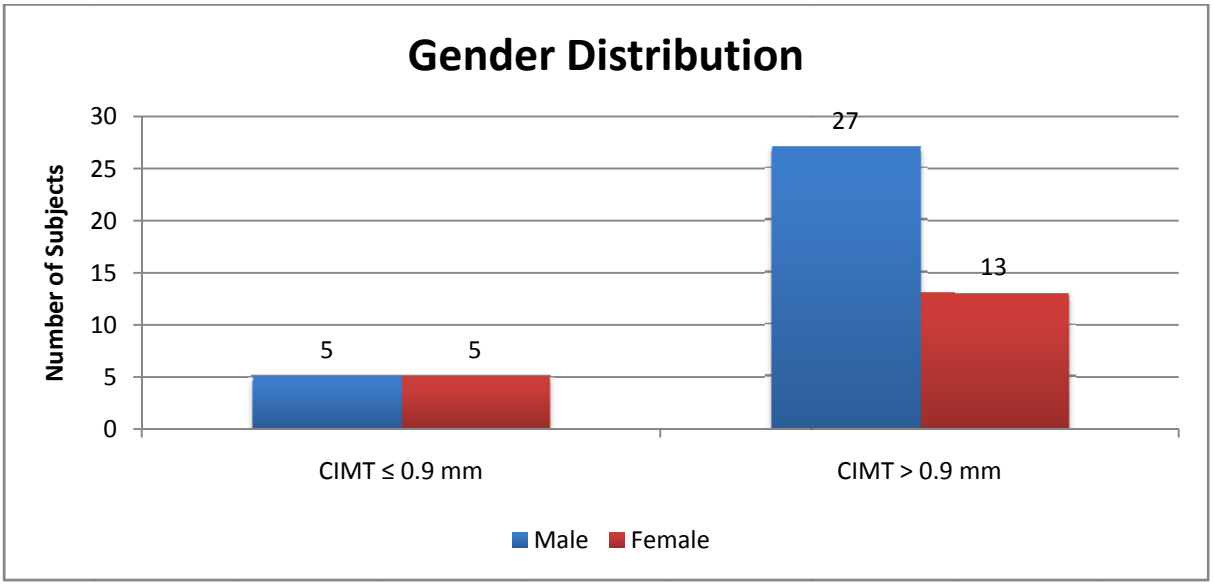


Age Distribution	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
≤ 40 years	4	40.00	17	42.50
41-50 years	4	40.00	20	50.00
51-60 years	2	20.00	3	7.50
Total	10	100	40	100

Age Distribution	CIMT ≤ 0.9 mm	CIMT > 0.9 mm
N	10	40
Mean	44.40	43.48
SD	6.95	5.90
P value Unpaired t Test		0.7049

Majority of the CIMT ≤ 0.9 mmg Group patients belonged to the 41-50 years age class interval (n=4, 40%) with a mean age of 44.40 years. In the CIMT > 0.9 mm group patients, majority belonged to the same age class interval (n=20, 50%) with a mean age of 43.48 years. The association between the study groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

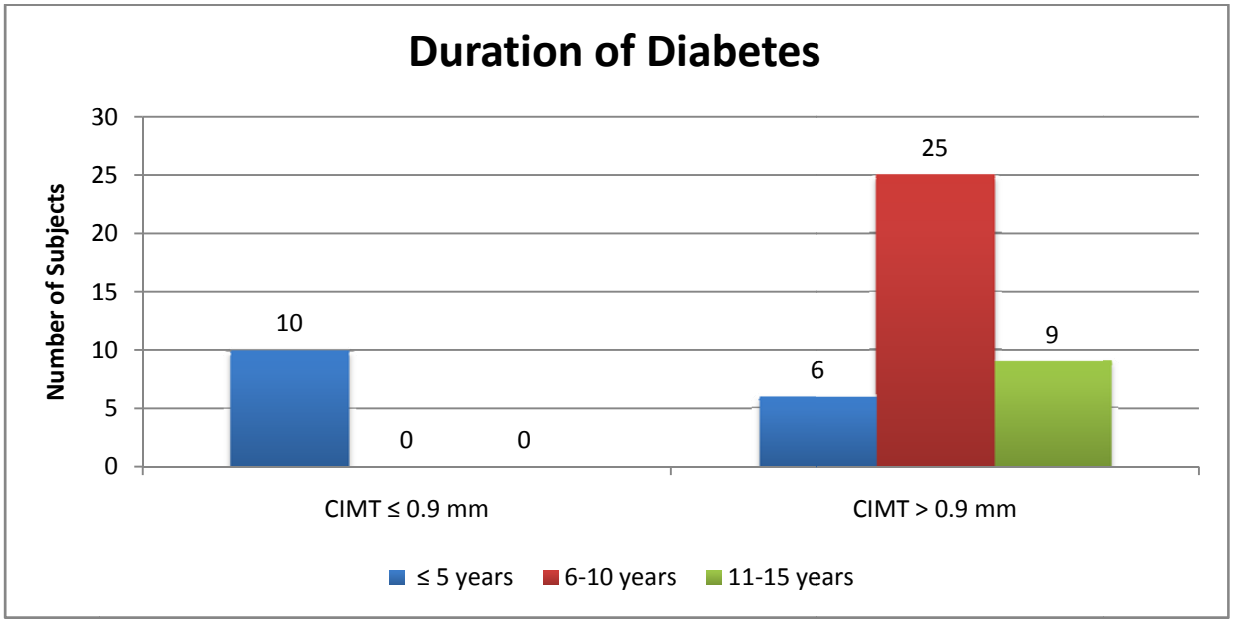
Gender



Gender Distribution	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
Male	5	50.00	27	67.50
Female	5	50.00	13	32.50
Total	10	100	40	100
P value Fishers Exact Test			0.4627	

Majority of the CIMT ≤ 0.9 mm group patients belonged to the male gender class interval (n=5, 50%). In the CIMT > 0.9 mm group patients, majority also belonged to the male gender class interval (n=27, 67.50%) . The association between the study groups and gender distribution is considered to be not statistically significant since p > 0.05 as per fishers exact test.

Duration of Diabetes



Duration of Diabetes	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
≤ 5 years	10	100.00	6	15.00
6-10 years	0	0.00	25	62.50
11-15 years	0	0.00	9	22.50
Total	10	100	40	100

Duration of Diabetes	CIMT ≤ 0.9 mm	CIMT > 0.9 mm
N	10	40
Mean	2.40	8.90
SD	0.84	3.25
P value Unpaired t Test		0.0000

Results

In patients belonging to CIMT ≤ 0.9 mm group, the mean duration of diabetes is 2.40 years. In CIMT > 0.9 mm group, the mean duration of diabetes is 8.90 years. The decreased mean duration of diabetes in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group is statistically significant as the p value is 0.0000 as per unpaired t- test indicating a true difference among study groups.

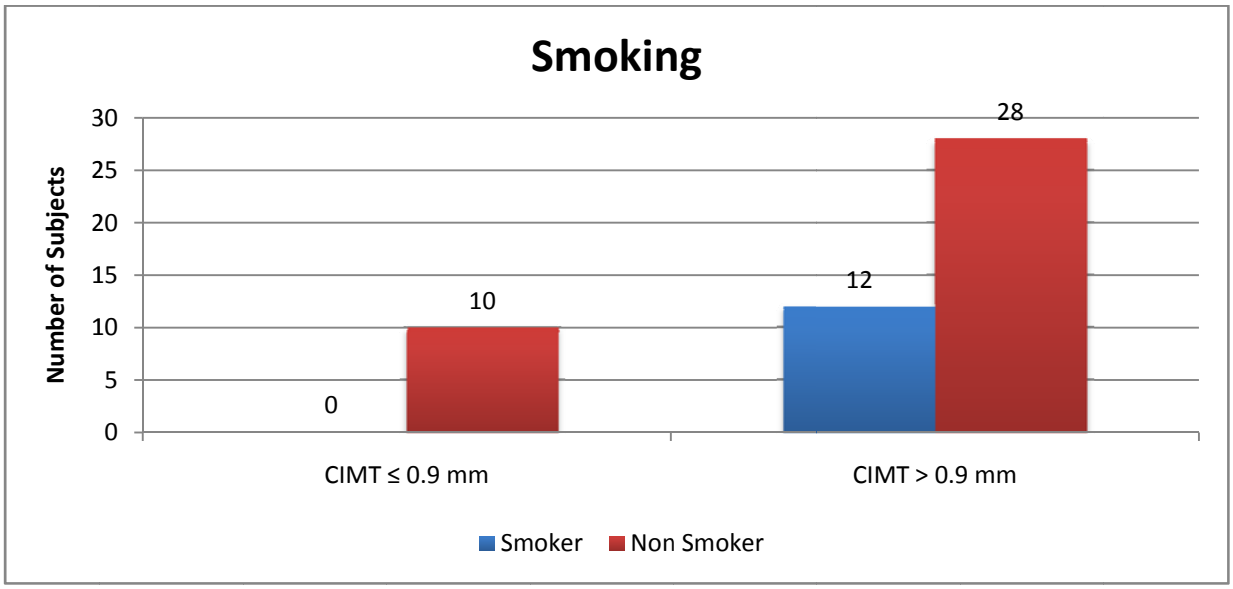
Discussion

The mean duration of diabetes was meaningfully less in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group by 6.50 years. This significant difference of 73 % decrease in mean duration of diabetes in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group is true and has not occurred by chance.

Conclusion

In this study we can safely conclude that mean duration of diabetes was significantly and consistently higher in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group. Hence we can infer that the incidence of CIMT > 0.9 mm increases with increasing duration of diabetes.

Smoking



Smoking	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
Smoker	0	0.00	12	30.00
Non Smoker	10	100.00	28	70.00
Total	10	100	40	100
P value Fishers Exact Test			0.0320	

Results

In patients belonging to CIMT ≤ 0.9 mm group, majority were non smokers (n=10, 100%). In CIMT > 0.9 mm group, majority too were non smokers (n=28, 70%). The increased incidence of smoking in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group is statistically significant as the p value is 0.0320 as per fishers exact test indicating a true difference among study groups.

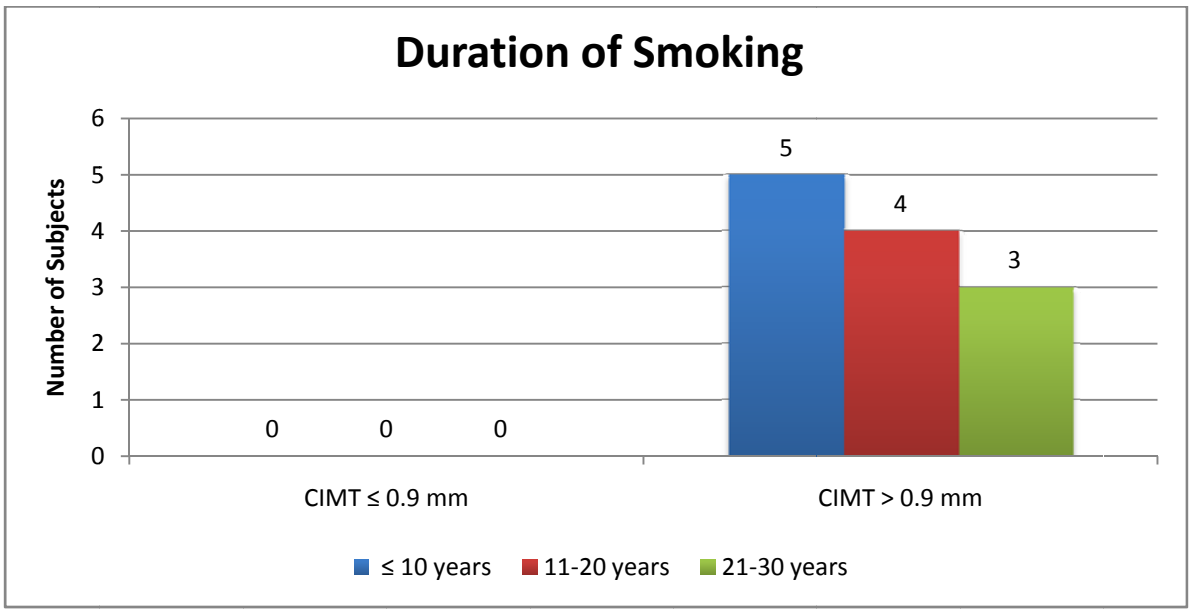
Discussion

The incidence of smoking was meaningfully more in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group by 30 percentage points. This significant difference of 1.43 times increase in incidence of smoking in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group is true and has not occurred by chance.

Conclusion

In this study we can safely conclude that incidence of smoking was significantly and consistently higher in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group. Hence we can infer that the incidence of CIMT > 0.9 mm increases among smokers.

Duration of Smoking

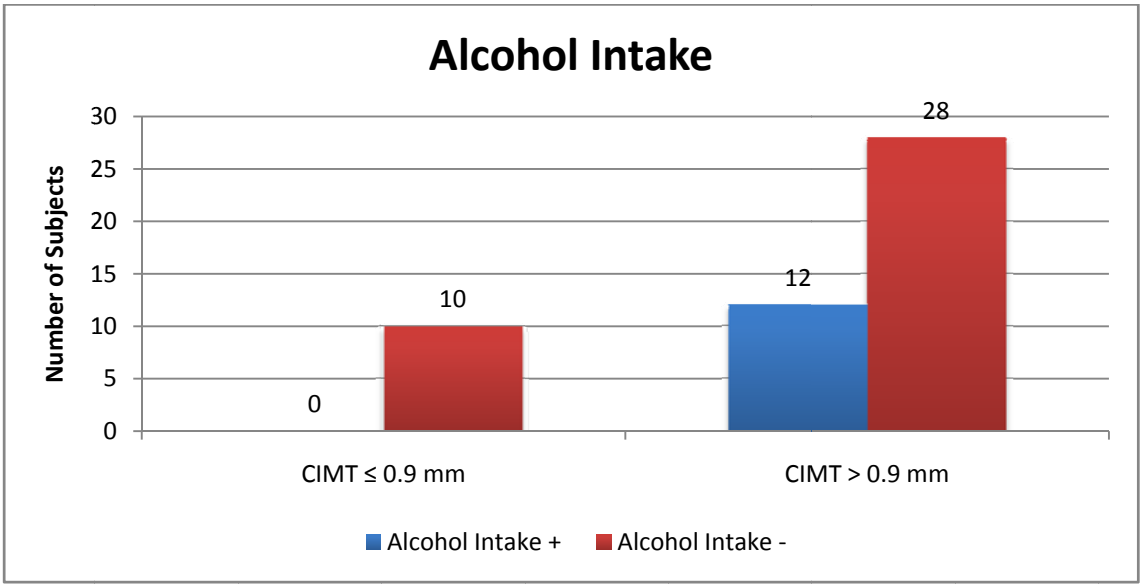


Duration of Smoking	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
≤ 10 years	0	0.00	5	12.50
11-20 years	0	0.00	4	10.00
21-30 years	0	0.00	3	7.50
Total	0	0	12	30

Duration of Smoking	CIMT ≤ 0.9 mm	CIMT > 0.9 mm
N	0	12
Mean	0.00	16.25
SD	0.00	7.72
P value Unpaired t Test		NA

By conventional criteria the association between the study groups and duration of smoking is considered to be not statistically significant since $p > 0.05$

Alcohol Intake



Alcohol Intake	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
Alcohol Intake +	0	0.00	12	30.00
Alcohol Intake -	10	100.00	28	70.00
Total	10	100	40	100
P value Fishers Exact Test			0.0420	

Results

In patients belonging to CIMT ≤ 0.9 mm group, majority were non alcoholics (n=10, 100%). In CIMT > 0.9 mm group, majority too were non alcoholics (n=28, 70%). The increased incidence of alcohol intake in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group is statistically significant as the p value is 0.0420 as per fishers exact test indicating a true difference among study groups.

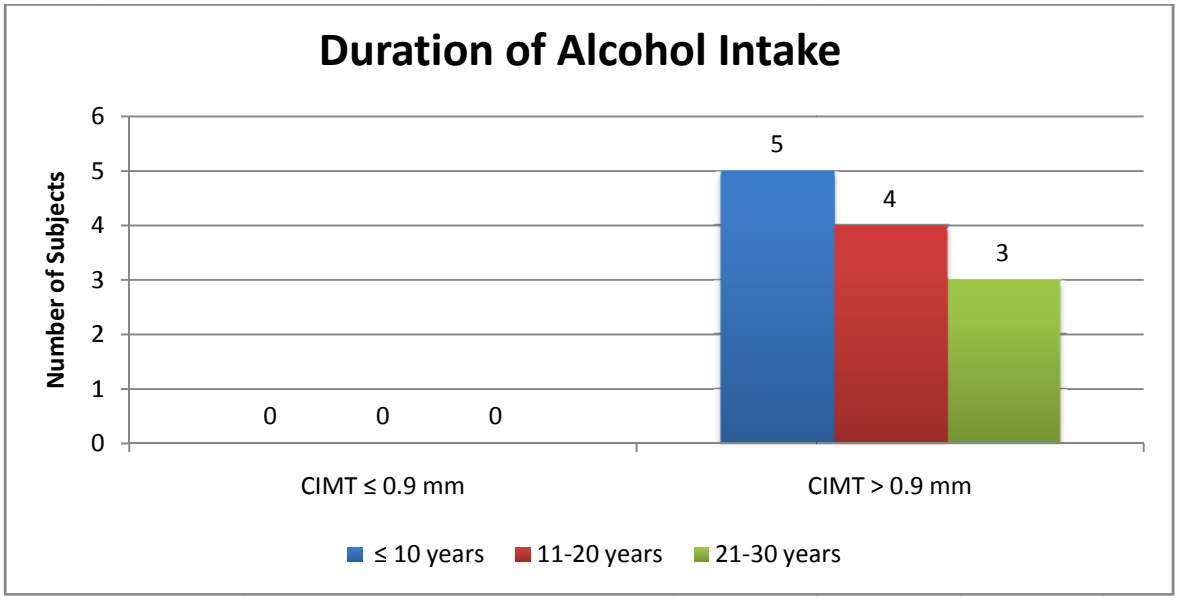
Discussion

The incidence of alcohol was meaningfully more in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group by 30 percentage points. This significant difference of 1.43 times increase in incidence of alcohol intake in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group is true and has not occurred by chance.

Conclusion

In this study we can safely conclude that incidence of alcohol intake was significantly and consistently higher in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group. Hence we can infer that the incidence of CIMT > 0.9 mm increases among subjects with the habit of alcohol intake.

Duration of Alcohol Intake

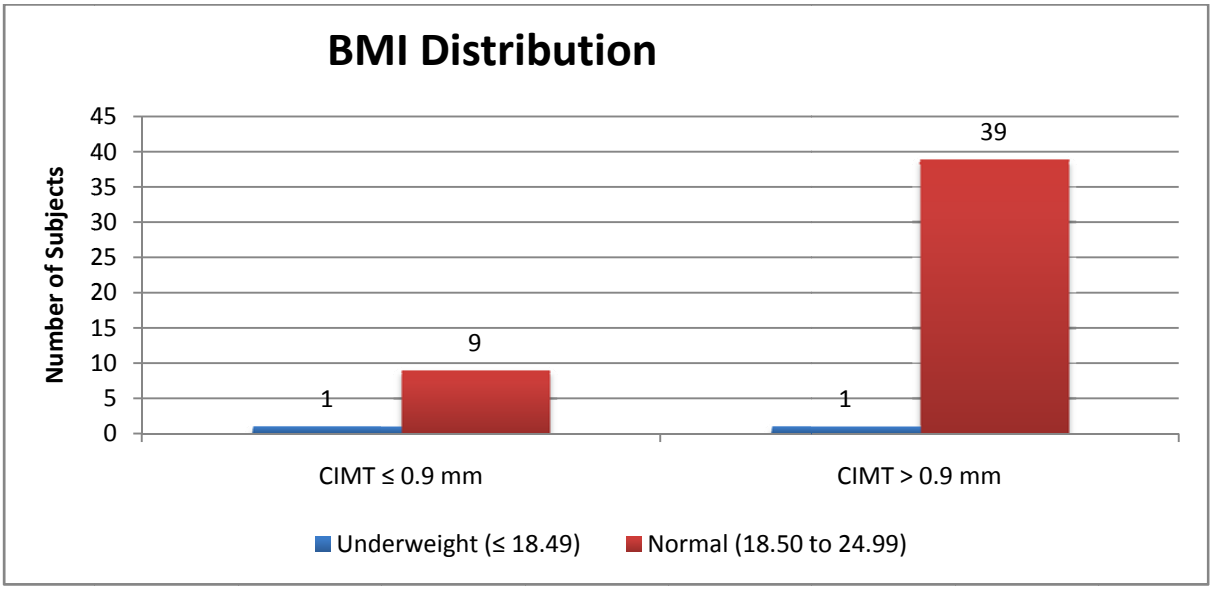


Duration of Alcohol Intake	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
≤ 10 years	0	0.00	5	12.50
11-20 years	0	0.00	4	10.00
21-30 years	0	0.00	3	7.50
Total	0	0	12	30

Duration of Alcohol Intake	CIMT ≤ 0.9 mm	CIMT > 0.9 mm
N	0	12
Mean	0.00	16.25
SD	0.00	7.83
P value Unpaired t Test		NA

By conventional criteria the association between the study groups and duration of alcohol intake is considered to be not statistically significant since $p > 0.05$

BMI

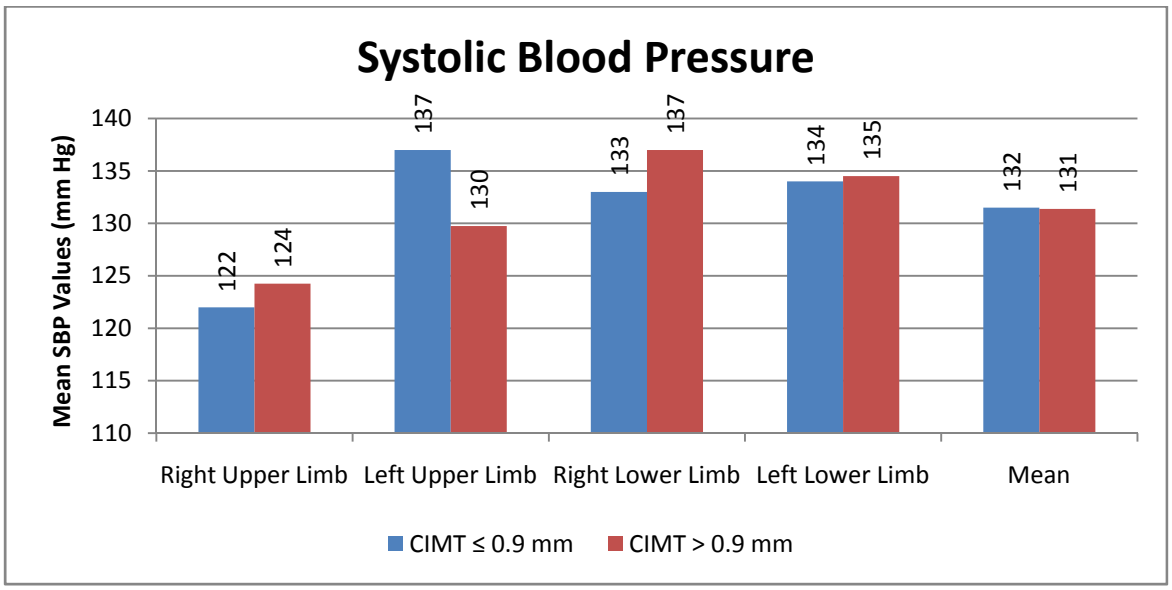


BMI Distribution	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
Underweight (≤ 18.49)	1	10.00	1	2.50
Normal (18.50 to 24.99)	9	90.00	39	97.50
Overweight (25 to 29.99)	0	0.00	0	0.00
Obese	0	0.00	0	0.00
Total	10	100	40	100

BMI Distribution	CIMT ≤ 0.9 mm	CIMT > 0.9 mm
N	10	40
Mean	20.95	21.39
SD	1.71	1.80
P value Unpaired t Test		0.4846

Majority of the CIMT ≤ 0.9 mmgGroup patients belonged to the normal BMI class interval (n=9, 90%) with a mean BMI of 20.95. In the CIMT > 0.9 mm group patients, majority belonged to the same BMI class interval (n=39, 97.50%) with a mean BMI of 21.39. The association between the study groups and BMI distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

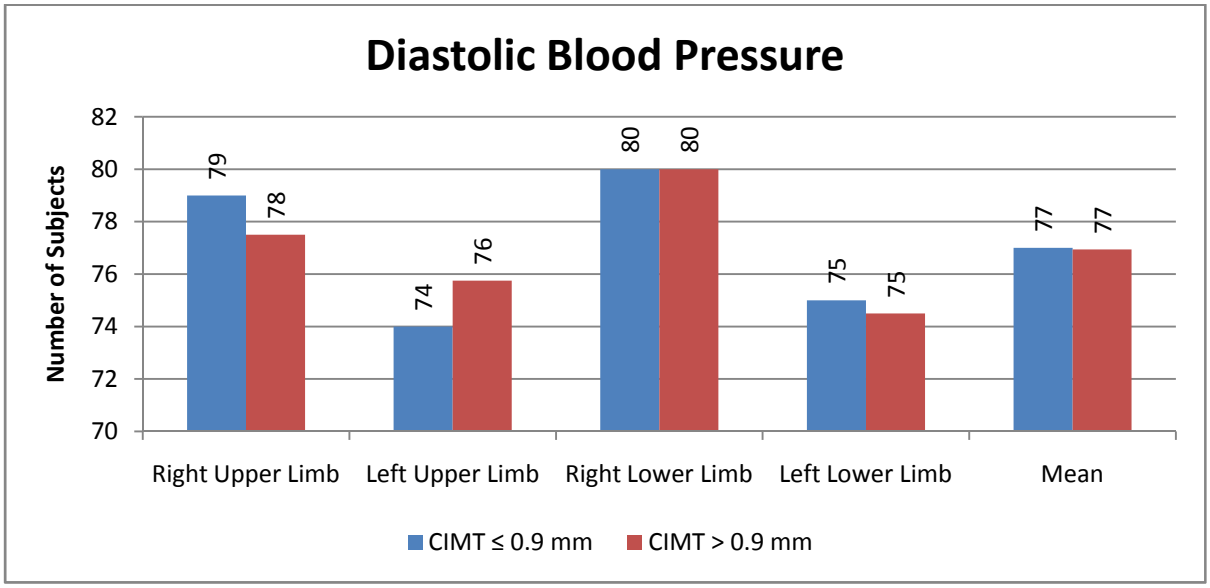
Systolic Blood Pressure



Systolic Blood Pressure		Right Upper Limb	Left Upper Limb	Right Lower Limb	Left Lower Limb	Mean
CIMT ≤ 0.9 mm	N	10	10	10	10	10
	Mean	122.00	137.00	133.00	134.00	131.50
	SD	11.35	9.49	9.49	5.16	5.30
CIMT > 0.9 mm	N	40	40	40	40	40
	Mean	124.25	129.75	137.00	134.50	131.38
	SD	11.96	12.30	4.64	5.04	5.69
P value Unpaired t Test		0.5877	0.0581	0.2241	0.7873	0.9485

Majority of the CIMT ≤ 0.9 mmg Group patients had a mean SBP of 132 mm Hg. . In the CIMT > 0.9 mm group patients had a mean SBP of 131 mm Hg The association between the study groups and systolic blood pressure distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

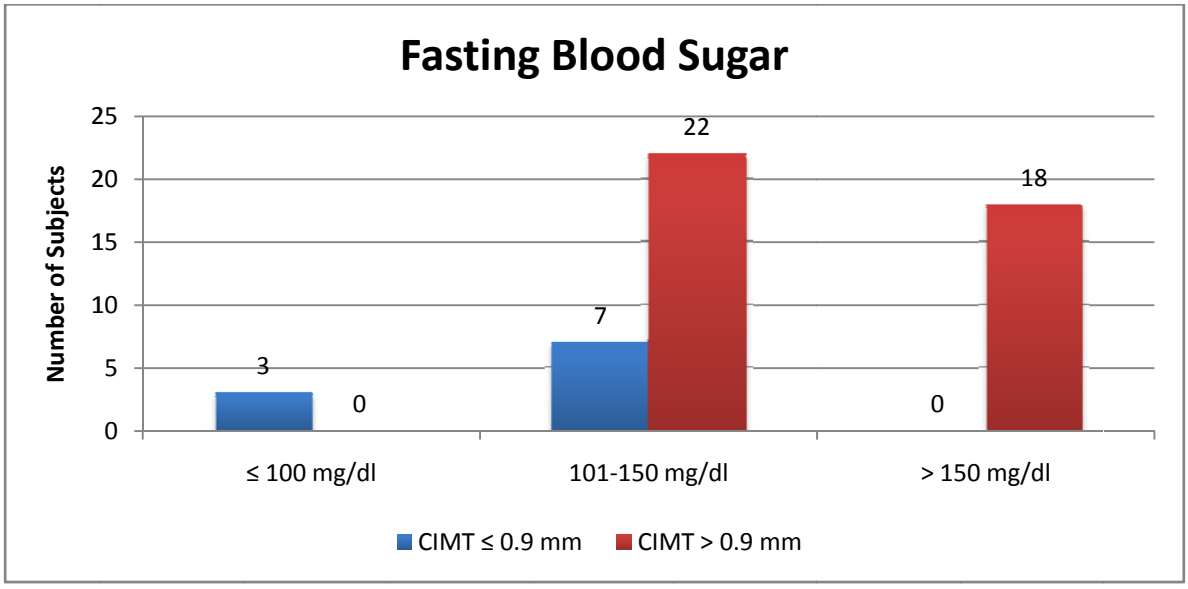
Diastolic Blood Pressure



Diastolic Blood Pressure		Right Upper Limb	Left Upper Limb	Right Lower Limb	Left Lower Limb	Mean
CIMT ≤ 0.9 mm	N	10	10	10	10	10
	Mean	79.00	74.00	80.00	75.00	77.00
	SD	3.16	5.16	0.00	5.27	1.58
CIMT > 0.9 mm	N	40	40	40	40	40
	Mean	77.50	75.75	80.00	74.50	76.94
	SD	4.39	5.01	0.00	5.04	2.80
P value Unpaired t Test		0.2329	0.3518	NA	0.7908	0.9262

Majority of the CIMT ≤ 0.9 mmg Group patients had a mean DBP of 77 mm Hg. . In the CIMT > 0.9 mm group patients had a mean DBP of 77 mm Hg The association between the study groups and diastolic blood pressure distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

Fasting Blood Sugar



Fasting Blood Sugar	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
≤ 100 mg/dl	3	30.00	0	0.00
101-150 mg/dl	7	70.00	22	55.00
> 150 mg/dl	0	0.00	18	45.00
Total	10	100	40	100

Fasting Blood Sugar	CIMT ≤ 0.9 mm	CIMT > 0.9 mm
N	10	40
Mean	105.60	148.23
SD	9.08	19.35
P value Unpaired t Test		0.0000

Results

In patients belonging to CIMT ≤ 0.9 mm group, the mean FBS is 105.60 mg/dl. In CIMT > 0.9 mm group, the mean FBS is 148.23 mg/dl. The decreased mean FBS in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group is statistically significant as the p value is 0.0000 as per unpaired t- test indicating a true difference among study groups.

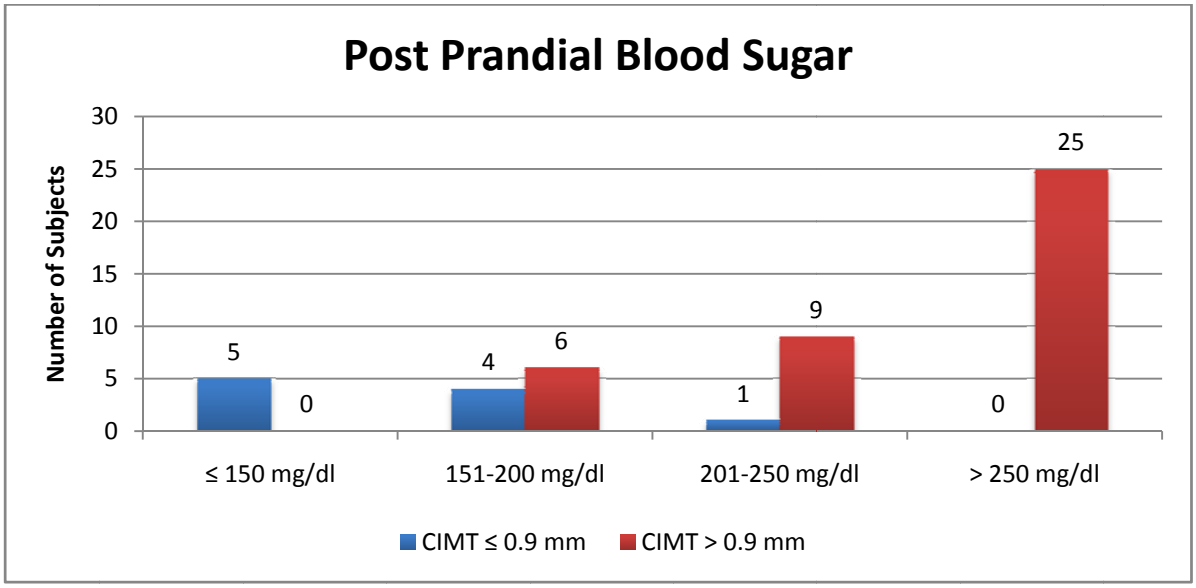
Discussion

The mean FBS was meaningfully less in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group by 42.63 mg/dl. This significant difference of 29 % decrease in mean FBS in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group is true and has not occurred by chance.

Conclusion

In this study we can safely conclude that mean fasting blood sugar was significantly and consistently higher in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group. Hence we can infer that the incidence of CIMT > 0.9 mm increases with increasing levels of FBS.

Post Prandial Blood Sugar



Post Prandial Blood Sugar	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%
≤ 150 mg/dl	5	50.00	0	0.00
151-200 mg/dl	4	40.00	6	15.00
201-250 mg/dl	1	10.00	9	22.50
> 250 mg/dl	0	0.00	25	62.50
Total	10	100	40	100

Post Prandial Blood Sugar	CIMT ≤ 0.9 mm	CIMT > 0.9 mm
N	10	40
Mean	155.40	253.38
SD	31.26	34.28
P value Unpaired t Test		0.0000

Results

In patients belonging to CIMT ≤ 0.9 mm group, the mean PPBS is 155.40 mg/dl. In CIMT > 0.9 mm group, the mean PPBS is 253.38 mg/dl. The decreased mean PPBS in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group is statistically significant as the p value is 0.0000 as per unpaired t- test indicating a true difference among study groups.

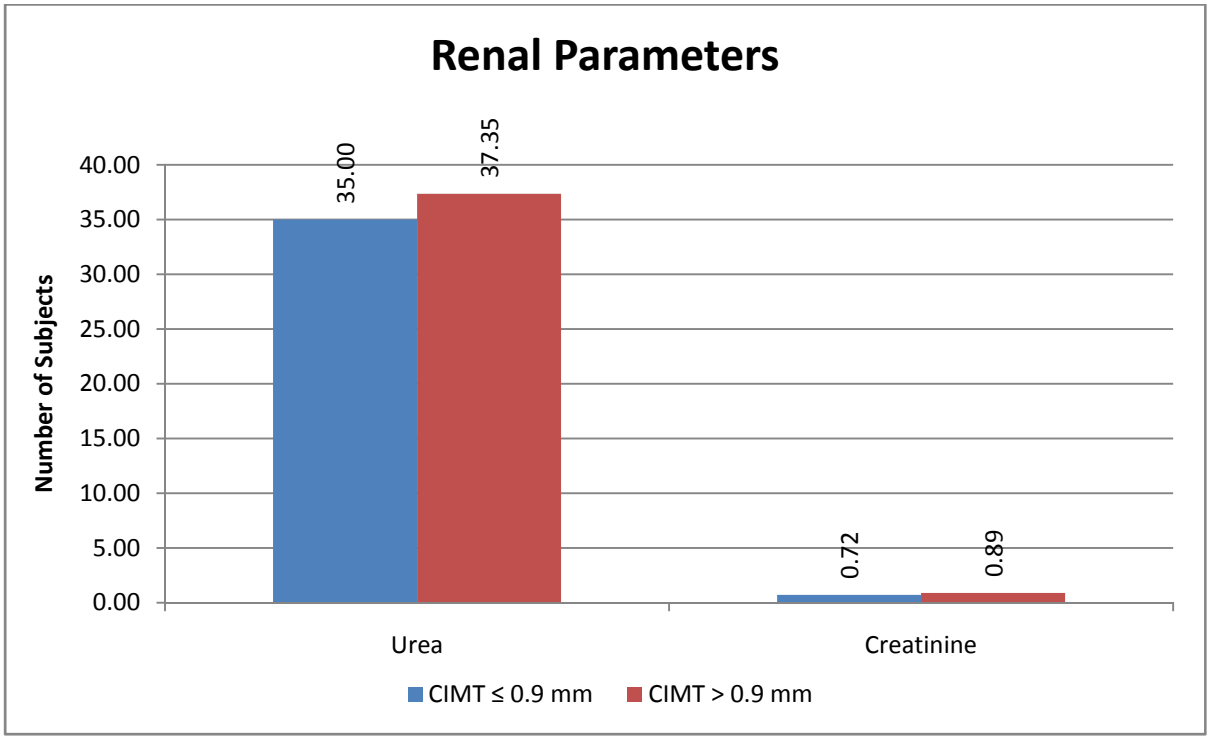
Discussion

The mean PPBS was meaningfully less in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group by 97.98 mg/dl. This significant difference of 39 % decrease in mean PPBS in CIMT ≤ 0.9 mm group compared to the CIMT > 0.9 mm group is true and has not occurred by chance.

Conclusion

In this study we can safely conclude that mean post prandial blood sugar was significantly and consistently higher in CIMT > 0.9 mm group compared to the CIMT ≤ 0.9 mm group. Hence we can infer that the incidence of CIMT > 0.9 mm increases with increasing levels of PPBS.

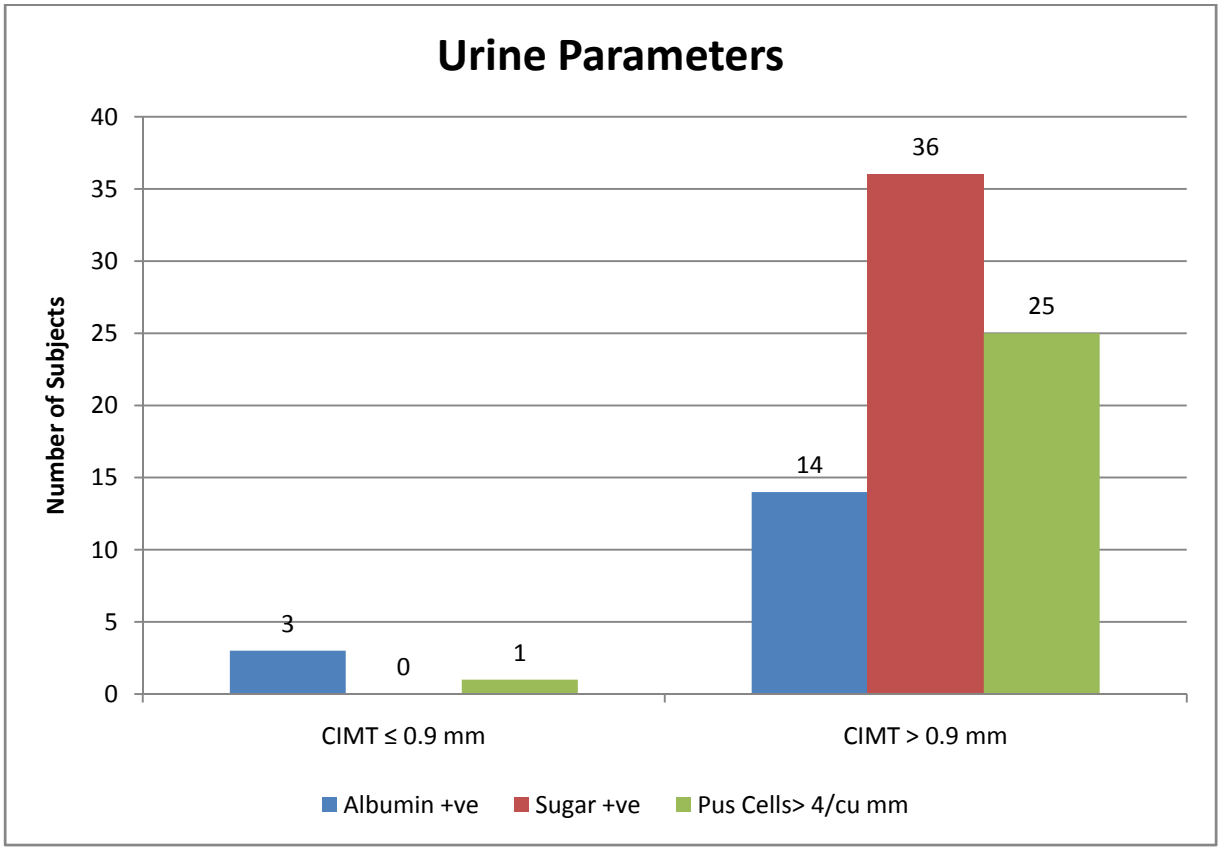
Renal Parameters



Renal Parameters		Urea	Creatinine
CIMT ≤ 0.9 mm	N	10	10
	Mean	35.00	0.72
	SD	3.30	0.09
CIMT > 0.9 mm	N	40	40
	Mean	37.35	0.89
	SD	3.77	0.22
P value Unpaired t Test		0.1489	0.2227

Majority of the CIMT ≤ 0.9 mmg Group patients had a mean blood urea levels of 35 mg/dl and mean serum creatinine levels of 0.72 mg/dl. In the CIMT > 0.9 mm group patients had a mean mean blood urea levels of 37.35 mg/dl and mean serum creatinine levels of 0.89 mg/dl. The association between the study groups and levels of blood urea and serum creatinine is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

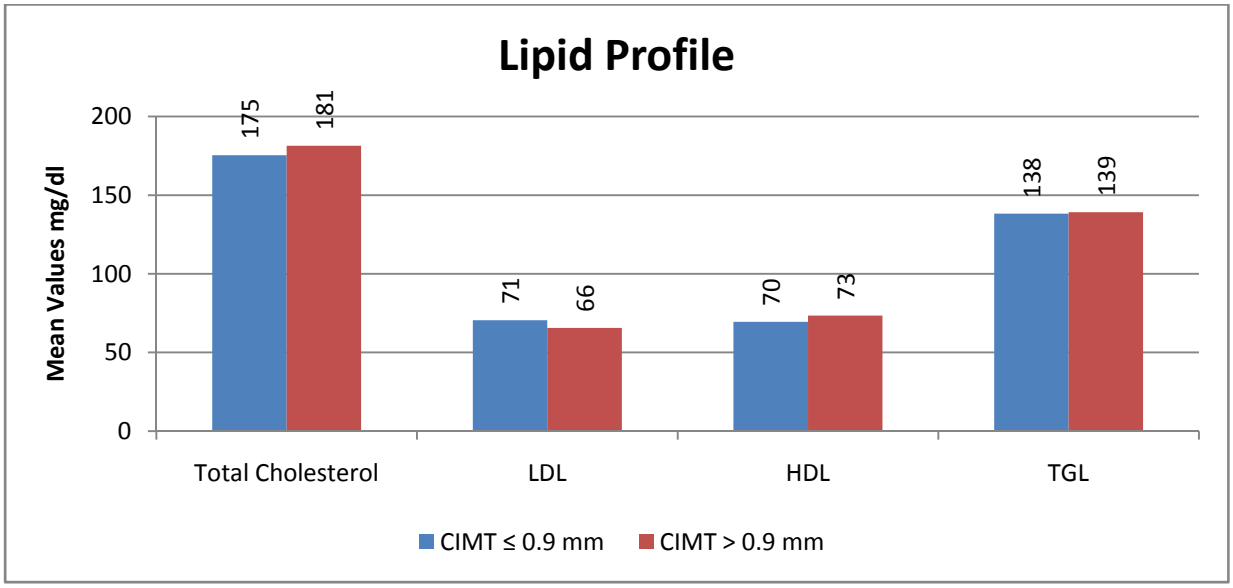
Urine Parameters



Urine Parameters	CIMT ≤ 0.9 mm	%	CIMT > 0.9 mm	%	P value Fishers Exact Test
Albumin +ve	3	30.00	14	35.00	0.9999
Sugar +ve	0	0.00	36	90.00	0.3671
Pus Cells> 4/cu mm	1	10.00	25	62.50	

Majority of the CIMT ≤ 0.9 mmg Group patients had urine albumin positive (n=3, 30%). In the CIMT > 0.9 mm group patients mainly had urine sugar positive (n=36, 90%). The association between the study groups urine test parameters is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

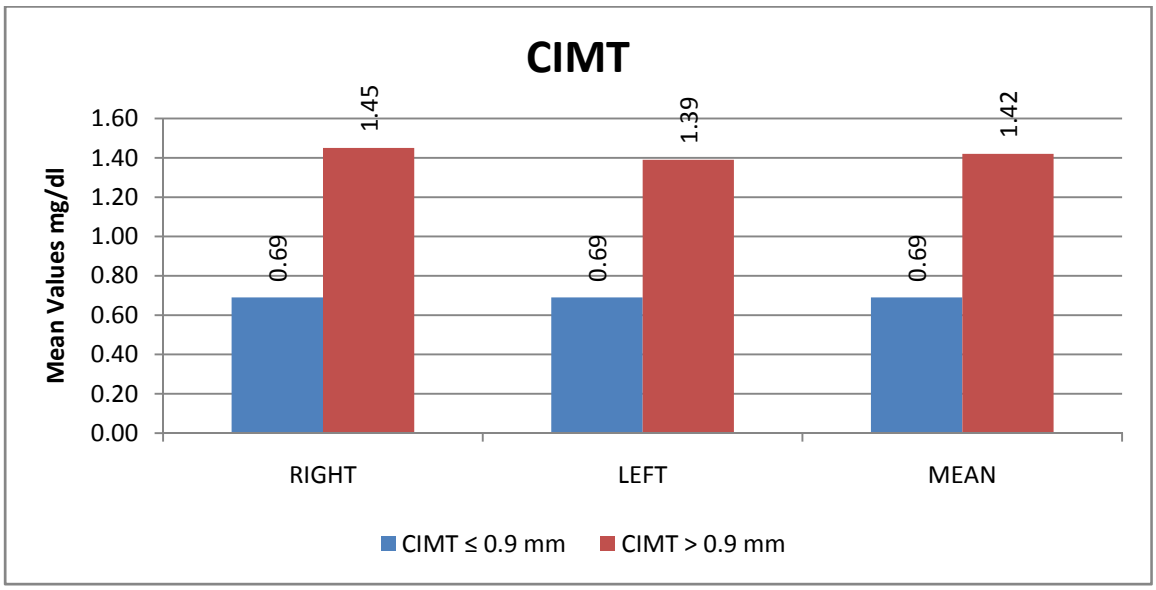
Lipid Profile



Lipid Profile		Total Cholesterol	LDL	HDL	TGL
CIMT ≤ 0.9 mm	N	10	10	10	10
	Mean	175.40	70.50	69.50	138.20
	SD	12.55	4.14	4.09	4.76
CIMT > 0.9 mm	N	40	40	40	40
	Mean	181.40	65.65	73.43	139.18
	SD	11.41	8.13	7.06	9.94
P value Unpaired t Test		0.1919	0.5132	0.0705	0.6571

Majority of the CIMT ≤ 0.9 mmg Group patients had a mean total cholesterol levels of 175.40 mg/dl, mean LDL levels of 70.50 mg/dl, mean HDL levels of 69.50 mg/dl and mean TGL levels of 138.20mg/dl. In the CIMT > 0.9 mm group patients had a mean total cholesterol levels of 181.40 mg/dl, mean LDL levels of 65.65 mg/dl, mean HDL levels of 73.43 mg/dl and mean TGL levels of 139.18 mg/dl. The association between the study groups and lipid profile parameters is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

CIMT



CIMT		RIGHT	LEFT	MEAN
CIMT ≤ 0.9 mm	N	10	10	10
	Mean	0.69	0.69	0.69
	SD	0.11	0.11	0.11
CIMT > 0.9 mm	N	40	40	40
	Mean	1.45	1.39	1.42
	SD	0.27	0.22	0.23

Multivariate logistic regression model for statistically Significant Predictor of immediate adverse event

Independent Variables	CIMT > 0.9 mm		
	Odds Ratio	95% Confidence Interval	P value
Age > 50 years	4.36	0.56-33.74	0.158
Gender - Male	1.91	0.33-38.4	0.216
Duration of Diabetes > 5 years	10.18	1.09-94.73	0.042*
Smoking	3.04	1.33-6.95	0.008*
Alcohol Intake	4.29	1.12-16.52	0.039*
FBS > 150 mg/dl	1.16	1.17-12.49	0.041*
PPBS > 250 mg/dl	3.58	1.15-11.13	0.043*

Multivariate analysis demonstrated that

- The risk of developing CIMT > 0.9 mm in patients with duration of diabetics > 5 years is 10.18 times significantly more than patients with duration of diabetics < 5 years. It is statistically significant with a p-value of 0.0042
- The risk of developing CIMT > 0.9 mm in patients in smokers is 3.04 times significantly more than in non smokers. It is statistically significant with a p-value of 0.008
- The risk of developing CIMT > 0.9 mm in patients with alcohol intake is 4.29 times significantly more than patients without alcohol intake. It is statistically significant with a p-value of 0.0039

- The risk of developing CIMT > 0.9 mm in patients with FBS > 150 mg/dl is 1.16 times significantly more than patients with FBS < 150 mg/dl. It is statistically significant with a p-value of 0.0041.
- The risk of developing CIMT > 0.9 mm in patients with PPBS > 250 mg/dl is 3.58 times significantly more than patients with PPBS < 250 mg/dl It is statistically significant with a p-value of 0.0043

CONCLUSION

1) We did not find any significant association between age and CIMT. As the mean age group was found to be almost same

2) There was no significant association between CIMT and gender distribution.

3) CIMT was significantly associated more with duration of diabetes(as the duration increased)

4) Smokers were found to be at higher risk of increase in CIMT than non-smokers.

5) Though the distribution of alcohol was equal among both the age groups, but CIMT was more significant among patient with diabetes and alcoholism. As our study group volume is small we could not prove the exact association between CIMT and alcohol intake.

6) In our study population BMI didn't show any significant association

7) Blood pressure was not found to be statistically significant in our study population

8) Patient with higher fasting and post prandial blood sugar value showed significant association with CIMT values.

9) Urine routine, renal parameters and lipid profile didn't show any significant correlation with carotid IMT in our study

10) As compared to the cited original articles which showed direct relation between diabetes and CIMT , my study population had around 80% diabetic patients with significant carotid CIMT values.

CIMT was more significant with increase in the duration of diabetes, altered fasting and post prandial glycemic status. This was similar to the original study article.

CIMT greater than 0.9mm was an individual marker of generalised atherosclerosis. Patients with these values are at higher risk for future cardiovascular events and newer or recurrent ischemic strokes.

80% of our study group comes under this high risk category.

Significant increase in carotid IMT was found with patients of smoking and alcohol. Possible explanation for this difference may be related to limited sample size of the study and ethnicity of the study subjects.

Thereby we conclude even in the absence of smoking and alcohol, normotension and normal lipid profile, independently type 2 DM was found to be associated with carotid IMT values than other components.

Further workup and prospective studies are needed with regards to

(1) To predict the trend of future cardiovascular events like CAD and ischemic strokes

(2) Regression of CIMT with management of type 2 DM patients.

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ABBREVIATIONS

1.TNF ALPHA	-	TUMOUR NECROSIS FACTOR ALPHA
2.TGF BETA	-	TRANSFORMING GROWTH FACTOR BETA
3.DKA	-	DIABETIC KETOACIDOSIS
4.HHS	-	HYPEROSMOLAR HYPERGLYCEMIC STATE
5.LDL	-	LOWDENSITY LIPOPROTEIN
6. HDL	-	HIGH DENSITY LIPOPROTEIN
7.OHA	-	ORAL HYPOGLYCEMIC AGENT
8.ACS	-	ACUTE CORONARY SYNDROMES
9.CIMT	-	CAROTID INTIMA MEDIA THICKNESS
10.GLP 1	-	GLUCAGON LIKE PEPTIDE
11.MODY	-	MATURITY ONSET DIABETES OF YOUNG
12.HBA1C	-	HAEMOGLOBIN A1C

- PROFORMA
- Name : Age : Sex : OP/IP No:
- Occupation :
- Address :
- Phone :
- Chief Complaints :
- HISTORY :
- h/o HTN
- h/o DM
- h/o smoking - duration pack years
- h/o alcoholism – duration quantity
- GENERAL EXAMINATION :
- Wt. - Ht. - BMI - WHR –
- Pallor Icterus Cyanosis Clubbing Pedal edema
- JVP Lymphadenopathy Xanthomas Skin tags Acanthosis
- VITALS :
- Pulse - Rate Rhythm Character Volume
- Carotids
- Femoral
- Radial
- Popliteal
- Brachial
- Post. Tibial
- Dorsalis pedis
- BP - Rt. UL
- Lt. UL

- Rt. LL
- Lt.LL
- RR –
- SYSTEMIC EXAMINATION-
- CVS :
- RS :
- P/A :
- CNS :
- INVESTIGATIONS :
-
- Blood Sugar – Fasting
- Post-prandial
-
- Blood Urea
-
- Serum creatinine
-
- Urine – Albumin Sugar Deposits
-
- Lipid Profile – TC LDL HDL VLDL TG
-
- ECG –
-
- CIMT – Rt. Lt. Mean CIMT –

INFORMED CONSENT

"CAROTID INTIMA MEDIA THICKNESS AS A MARKER OF PRECLINICAL ATHEROSCLEROSIS IN TYPE 2 DIABETES MELLITUS"

AT GOVERNMENT STANLEYMEDICAL COLLEGE HOSPITAL, CHENNAI.

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

“கரோட்டிட், நெருங்கிய ஊடக தடிமன் நீரிழிவு பெருந்தமனி தடிப்பு ஒரு மார்க்கர்”

நான் இந்த ஆராய்ச்சி விவரங்களை முற்றிலும் புரிந்துகொண்டேன்.ஆய்வில் பங்கேற்கும் போது, சாத்தியமானஅபாயங்கள்மற்றும்பயன்களைபற்றிநான் அறிந்துளளேன்.நான்எந்தவொருவேளையிலும்ஆய்வில்இருந்து திரும்பமுடியும்,அதன்பின்னர்,நான்வழக்கம்போல்மருத்துவ சிகிச்சைபெறமுடியும்என்றுபுரிந்துகொள்கிறேன்

நான்ஆய்வில்பங்குஎடுத்துபணம்எதையும்பெறமுடியாதுஎன்று அறிந்துள்ளேன்.இந்தஆய்வின்முடிவுகள்எந்தமெடிக்கல்ஜர்னலில் வெளியிடப்படஇருந்தால்நான்எதிர்க்கவில்லை,என்தனிப்பட்ட அடையாளத்தைவெளிப்படுத்தப்பட்டுஇருக்ககூடாது.

நான்இந்தஆய்வில்பங்கெடுப்பதன்மூலம்நான்என்னசெய்ய போகிறேன்என்றுதெரியும்

நான்இந்தஆய்வில்என்முழுஒத்துழைப்பையும்கொடுப்பேன்என்று உறுதியளிக்கிறேன்.

தன்னார்வளர் சாட்சி

பெயர்மற்றும்முகவரி

பெயர்மற்றும்முகவரி

கையொப்பம் / விரல்ரேகை: கையொப்பம் / விரல்ரேகை:

ஆராய்ச்சியாளராக

கையொப்பம்மற்றும்தேதி

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Carotid Intima media Thickness as a marker of preclinical Atherosclerosis in type 2 Diabetes mellitus.

Principal Investigator : Dr. Ayyappan.G

Designation : PG in MD (General Medicine)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 25.03.2015 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

Sl.no	NAME	AGE	SEX	DM	DURATION(yrs)	HT	SMOKING	SMOKING DURATION	ALCOHOL	ALCOHOL DURATION	BMI	BP				FBS	PPBS	UREA	CREATININE	URINE			LIPID PROFILE				CIMT		
												RUL	LUL	RLL	LLL					ALBUMIN	SUGAR	DEPOSITS	T. CHOLESTEROL	LDL	HDL	TGL	RIGHT	LEFT	MEAN
1	RAJU	40	M	yes	5	no	no		no		24	140/80	130/80	140/80	140/80	123	180	42	0.9	1+	nil	4-6pus cells	192	100	60	154	1.2	1.2	1.2
2	SHANKAR	38	M	yes	2	no	no		no		22	130/80	140/70	140/80	140/80	98	132	36	0.8	1+	nil	2-3pus cells	160	70	68	140	0.8	0.8	0.8
3	MEENA	35	F	yes	2	no	no		no		22	120/70	110/70	140/80	130/70	106	146	38	0.7	nil	nil	1-2pus cells	170	65	70	132	0.7	0.7	0.7
4	KUMAR	36	M	yes	10	no	no		no		20	110/80	140/80	130/80	130/70	180	250	46	1	2+	2+	4-6pus cells	188	68	74	144	1.2	1.4	1.3
5	SELVI	42	F	yes	1	no	no		no		23	140/80	140/70	110/80	130/80	110	132	28	0.5	nil	nil	4-6pus cells	160	74	66	138	0.8	0.8	0.8
6	VASANTHA	50	M	yes	4	no	no		no		22	130/80	140/70	140/80	140/80	90	124	32	0.7	nil	nil	no deposits	190	76	68	144	0.6	0.6	0.6
7	RAJESH	48	M	yes	10	no	yes	10 years	yes	10 years	19	140/80	130/80	140/80	140/80	140	172	42	0.8	nil	nil	no deposits	174	64	66	126	1.8	1.4	1.6
8	KUMARI	38	F	yes	8	no	no		no		20	120/70	110/70	140/80	130/70	136	250	38	0.7	1+	2+	4-6pus cells	138	62	65	145	1	1	1
9	AADHI	45	M	yes	6	no	yes	30 years	yes	30 years	23	110/80	140/80	130/80	130/70	180	286	40	0.7	1+	2+	6-8pus cells	170	66	86	110	1.7	1.7	1.7
10	SHANMUGA	56	M	yes	15	no	yes	15 years	yes	15 years	24	140/80	130/80	140/80	140/80	176	274	46	0.8	1+	2+	6-8pus cells	180	64	76	118	1.6	1.6	1.6
11	MURUGAN	49	M	yes	10	no	no		no		20	140/80	130/80	140/80	140/80	170	280	36	0.5	1+	2+	6-8pus cells	190	72	82	138	1	1	1
12	DHANRAJ	43	M	yes	6	no	yes	10 years	yes	10 years	18	110/80	140/80	130/80	130/70	160	260	38	0.7	1+	2+	4-6pus cells	166	68	80	146	1.4	1.4	1.4
13	AANDAAL	42	F	yes	8	no	no		no		19	130/80	140/70	140/80	140/80	160	240	40	1.2	1+	2+	4-6pus cells	186	54	68	124	1.3	1.3	1.3
14	MUNIYAMM	40	F	yes	5	no	no		no		22	120/70	110/70	140/80	130/70	116	170	38	0.8	nil	NIL	no deposits	190	68	84	148	1.2	1.2	1.2
15	BALU	38	M	yes	12	no	yes	10 years	yes	10 years	23	140/80	130/80	140/80	140/80	132	190	36	0.9	nil	1+	no deposits	180	56	68	146	1.8	1.4	1.6

16	GANESH	36	M	yes	10	no	no		no		20	120/70	110/70	140/80	130/70	146	266	40	1	1+	2+	4-6pus cells	166	68	70	138	1.6	1.6	1.6
17	VIDHYA	39	F	yes	3	no	no		no		18	110/80	140/80	130/80	130/70	96	160	38	0.7	nil	nil	no deposits	180	76	68	136	0.7	0.7	0.7
18	CHELLAMA	48	F	yes	2	no	no		no		20	130/80	140/70	140/80	140/80	104	162	36	0.8	nil	nil	no deposits	196	72	65	140	0.8	0.8	0.8
19	MARY	50	F	yes	15	no	no		no		22	140/80	130/80	140/80	140/80	170	280	38	0.6	1+	2+	4-6pus cells	170	58	80	130	1.5	1.5	1.5
20	JOHN	55	M	yes	3	no	no		no		19	110/80	140/80	130/80	130/70	122	176	32	0.7	nil	nil	no deposits	180	68	72	132	0.6	0.6	0.6
21	VELU	48	M	yes	5	no	no		no		24	120/70	110/70	140/80	130/70	160	286	34	1.2	nil	2+	4-6pus cells	180	62	74	146	1.6	1.2	1.4
22	DAVID	46	M	yes	8	no	yes	25 years	yes	25 years	23	130/80	140/70	140/80	140/80	130	284	36	0.9	nil	2+	4-6pus cells	190	66	72	138	1.8	1.4	1.6
23	RAHMAN	48	M	yes	6	no	yes	30 years	yes	30 years	22	110/80	140/80	130/80	130/70	160	250	38	1.2	nil	2+	4-6pus cells	192	64	78	146	1.7	1.7	1.7
24	KUPPAMMA	38	F	yes	7	no	no		no		21.5	120/70	110/70	140/80	130/70	180	270	40	0.8	1+	2+	6-8pus cells	176	66	74	138	1.4	1.4	1.4
25	KANNAN	40	M	yes	2	no	no		no		20.5	110/80	140/80	130/80	130/70	110	230	36	0.8	nil	ni	no deposits	164	72	66	134	0.8	0.8	0.8
26	MURALI	44	M	yes	5	no	no		no		19	130/80	140/70	140/80	140/80	140	270	32	0.7	nil	2+	1-2pus cells	188	66	72	148	1.6	1.6	1.6
27	GOWRI	46	F	yes	10	no	no		no		22	110/80	140/80	130/80	130/70	156	280	38	0.7	nil	3+	2-3pus cells	194	60	84	146	1.7	1.7	1.7
28	SRIDEVI	48	F	yes	14	no	no		no		23	130/80	140/70	140/80	140/80	130	250	36	0.8	nil	2+	2-3pus cells	174	60	66	136	1.5	1.5	1.5
29	RAMAN	38	M	yes	12	no	no		no		20	110/80	140/80	130/80	130/70	110	246	40	0.8	nil	2+	4-6pus cells	170	62	65	148	1.6	1.6	1.6
30	MUNUSAMY	39	M	yes	15	no	no		no		24	140/80	130/80	140/80	140/80	160	280	38	0.7	nil	2+	4-6pus cells	192	60	72	130	1.2	1.2	1.2
31	LAKSHMI	54	F	yes	5	no	no		no		22	110/80	140/80	130/80	130/70	170	276	40	1.2	nil	2+	4-6pus cells	186	90	64	136	1	1	1
32	PRAKASH	36	M	yes	8	no	yes	10 years	yes	18 years	20	130/80	140/70	140/80	140/80	166	250	30	1	nil	2+	no deposits	180	56	66	144	1.8	1.4	1.6
33	MANIKAND	48	M	yes	6	no	no		no		21	120/70	110/70	140/80	130/70	140	270	28	0.6	nil	2+	4-6pus cells	190	66	72	138	1.7	1.7	1.7
34	VENKATESI	49	M	yes	12	no	no		no		19	110/80	140/80	130/80	130/70	160	256	36	0.9	nil	2+	4-6pus cells	192	62	66	146	1.4	1.4	1.4

35	KRISHNAN	44	M	yes	10	no	yes	15 years	yes	15 years	20	140/80	130/80	140/80	140/80	140	280	38	0.6	nil	2+	no deposits	186	54	67	148	1.5	1.5	1.5
36	KAMATCHI	42	F	yes	15	no	no		no		22	120/70	110/70	140/80	130/70	138	266	34	1.2	nil	2+	4-6pus cells	190	66	72	138	1.7	1.7	1.7
37	VADIVEL	38	M	yes	8	no	no		no		24	110/80	140/80	130/80	130/70	140	270	40	1.2	1+	2+	4-6pus cells	176	66	72	136	1	1	1
38	ARUMUGAN	40	M	yes	6	no	yes	15 years	yes	12 years	23	110/80	140/80	130/80	130/70	150	280	34	0.6	1+	2+	6-8pus cells	188	68	74	144	1.8	1.4	1.6
39	UMA	38	F	yes	8	no	no		no		20.5	120/70	110/70	140/80	130/70	160	270	36	1.2	1+	2+	no deposits	190	72	82	138	1.5	1.5	1.5
40	MAHESWAR	36	F	yes	10	no	no		no		19.5	130/80	140/70	140/80	140/80	156	285	34	0.9	nil	2+	4-6pus cells	180	64	76	146	1	1	1
41	RAJA	56	M	yes	15	no	yes	15 years	yes	10 years	22	140/80	130/80	140/80	140/80	140	270	38	0.8	nil	2+	no deposits	192	64	76	144	1.6	1.6	1.6
42	ANTHONY	54	M	yes	3	no	no		no		23	110/80	140/80	130/80	130/70	110	132	36	0.8	1+	nil	2-3pus cells	170	66	74	140	0.5	0.5	0.5
43	NOOR MOH	36	M	yes	5	no	yes	10 years	yes	10 years	20	130/80	140/70	140/80	140/80	140	170	36	0.9	nil	nil	no deposits	170	66	86	110	1.5	1.5	1.5
44	LOORDH MA	48	F	yes	6	no	no		no		19	120/70	110/70	140/80	130/70	136	250	40	1.2	nil	2+	4-6pus cells	188	68	74	144	1.3	1.3	1.3
45	ANAND	50	M	yes	8	no	no		no		22	110/80	140/80	130/80	130/70	132	190	38	0.6	nil	nil	no deposits	170	66	84	140	1	1	1
46	SARAVANA	48	M	yes	10	no	no		no		24	120/70	110/70	140/80	130/70	104	262	40	1.2	nil	2+	no deposits	188	66	76	144	1.2	1.2	1.2
47	MAHALAKS	34	F	yes	8	no	no		no		21	140/80	130/80	140/80	140/80	170	260	34	1	nil	2+	no deposits	190	64	66	140	1.8	1.4	1.6
48	NEELAVENI	43	F	yes	2	no	no		no		20	130/80	140/70	140/80	140/80	110	160	38	0.7	1+	nil	2-3pus cells	184	66	78	146	0.6	0.6	0.6
49	KUMARESH	40	M	yes	6	no	no		no		24	110/80	140/80	130/80	130/70	140	250	30	0.8	nil	2+	4-6pus cells	164	66	64	146	1.2	1.4	1.3
50	BALAJI	46	M	yes	8	no	no		no		20	140/80	130/80	140/80	140/80	132	266	36	1.2	nil	2+	no deposits	190	68	84	142	1.6	1.6	1.6

ABBREVIATIONS

1.TNF ALPHA	-	TUMOUR NECROSIS FACTOR ALPHA
2.TGF BETA	-	TRANSFORMING GROWTH FACTOR BETA
3.DKA	-	DIABETIC KETOACIDOSIS
4.HHS	-	HYPEROSMOLAR HYPERGLYCEMIC STATE
5.LDL	-	LOWDENSITY LIPOPROTEIN
6. HDL	-	HIGH DENSITY LIPOPROTEIN
7.OHA	-	ORAL HYPOGLYCEMIC AGENT
8.ACS	-	ACUTE CORONARY SYNDROMES
9.CIMT	-	CAROTID INTIMA MEDIA THICKNESS
10.GLP 1	-	GLUCAGON LIKE PEPTIDE
11.MODY	-	MATURITY ONSET DIABETES OF YOUNG
12.HBA1C	-	HAEMOGLOBIN A1C